Dibenzoxazepines

The present invention relates to compounds, processes for their preparation, pharmaceutical compositions comprising them, and the use thereof for the treatment and/or prophylaxis of disorders in humans or animals, especially of cardiovascular disorders, e.g. of atherosclerosis.

Dibenzoxazepines are described in WO 00/48603 as $\alpha_V\beta_3$, $\alpha_V\beta_5$ and/or $\alpha_V\beta_6$ integrin receptor antagonists inter alia for the treatment of atherosclerosis. WO 99/11626 describes dibenzoxazepines as fibrinogen and/or vitronectin receptor antagonists inter alia for the treatment of atherosclerosis.

EP-A 419 861 describes the use of dibenzoxazepines for the treatment and/or prophylaxis of AIDS.

US 4,728,735 claims dibenzothiazepines for the treatment of cardiovascular disorders.

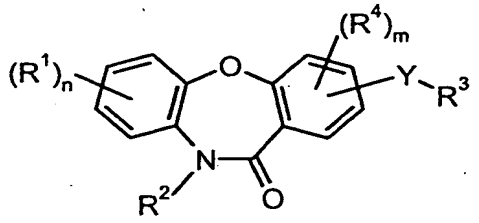
Anti-gastric ulcer dibenzoxazepinones are described in *CAPLUS* **1982**, 423831 (JP-A-57002278) and *CAPLUS* **1984**, 191915 (JP-A-58225073).

The inflammatory component in the pathophysiology of atherosclerosis is now generally acknowledged. These inflammatory vascular changes are characterized inter alia by migration of monocytes and increased release of proinflammatory cytokines. In particular, the formation of foam cells from the monocytes which have migrated in, and the altered metabolism of these foam cells, is central to plaque development and stability. It was possible to show that macrophages change their gene expression greatly under lipid loading. Increased expression of aminopeptidase N is particularly prominent in this connection.

Aminopeptidase N is a transmembrane ectoenzyme (EC 3.4.11.12) which is identical to the CD13 antigen. Aminopeptidase N catalyses the N-terminal elimination of amino acids, with preference for neutral amino acid residues. In synaptic membranes, aminopeptidase N thus inactivates neuropeptide hormones such as endorphins and encephalins. Further substrates include kinins, chemotactic peptides (MCP-1) and constituents of the extracellular matrix. Many publications indicate that aminopeptidase N is involved in the vascularization and spread of tumours. Membrane proteases are able to display their biological effect not only via cleavage of proteins but also via signal transduction processes. It has been possible to demonstrate that aminopeptidase N is linked to signal transduction in monocytes (Santos et al., Cellular Immunology **2000**, *201*, 22-32).

Strong expression of aminopeptidase N under conditions which resemble foam cell formation, and the involvement of aminopeptidase N in inflammatory processes of lymphocytes and monocytes indicate that inhibition of aminopeptidase N will lead to protective effects on the vessel wall, and will have a beneficial influence on plaque development and plaque stability.

The present invention therefore relates to compounds of the formula



(I),

in which

Y is a C_1-C_6-alkylene chain which optionally contains one or more double or triple bonds, in which one or more carbon atoms are optionally oxo-substituted and in which one or more carbon atoms are optionally replaced independently of one another by a nitrogen, oxygen or sulphur atom, it being

necessary for at least one carbon atom to be present between the heteroatom in Y and R^3, and it being necessary for at least one carbon atom to be present between two heteroatoms in Y,

R^1 is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl or alkylaminocarbonyl,

where alkoxycarbonyl and alkylaminocarbonyl may be substituted by 0, 1 or 2 substituents, where the substituents are selected independently of one another from the group consisting of alkoxy, aryl, heteroaryl, cycloalkyl, heterocyclyl and trimethylsilyl,

n is a number 0, 1, 2 or 3,

where if n is 2 or 3 the R^1 radicals may be identical or different,

R^2 is alkyl,

where alkyl may be substituted by 0, 1 or 2 substituents, where the substituents are selected independently of one another from the group consisting of halogen, hydroxyl, oxo, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, aryl, heteroaryl, cycloalkyl, heterocyclyl and heterocyclylcarbonyl,

where aryl, heteroaryl, cycloalkyl and heterocyclyl may be substituted by 0, 1, 2 or 3 substituents, where the substituents are selected independently of one another from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^3 is hydroxyl or amino,

R^4 is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl or alkylaminocarbonyl,

m is a number 0, 1 or 2,

where if m is 2 the R^4 radicals may be identical or different,

and the salts thereof, the solvates thereof and the solvates of the salts thereof.

Compounds according to the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, and the compounds encompassed by formula (I) and mentioned hereinafter as exemplary embodiment(s), and their salts, solvates and solvates of the salts where the compounds encompassed by formula (I) and mentioned hereinafter are not already salts, solvates and solvates of the salts.

The compounds according to the invention may, depending on their structure, exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers and diastereomers and respective mixtures thereof. The stereoisomerically pure constituents can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

The invention also relates, depending on the structure of the compounds, to tautomers of the compounds.

Salts which are preferred for the purposes of the invention are physiologically acceptable salts of the compounds according to the invention.

Physiologically acceptable salts of the compounds (I) encompass acid addition salts of mineral acids, carboxylic acids and sulphonic acids, e.g. salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds (I) also encompass salts of conventional bases such as by way of example and preferably alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 C atoms, such as by way of example and preferably ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine.

Solvates refer for the purposes of the invention to those forms of the compounds which form a complex in the solid or liquid state through coordination with solvent molecules. Hydrates are a specific form of solvates where the coordination takes place with water.

For the purposes of the present invention, the substituents have, unless specified otherwise, the following meaning:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkylaminocarbonyl and alkoxycarbonyl stand for a linear or branched alkyl radical having 1 to 8 carbon atoms, usually 1 to 6, preferably 1 to 4, particularly preferably 1 to 3 carbon atoms, by way of example and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkylene stands for a straight-chain or branched alkylene radical which optionally contains one or more double or triple bonds, in which one or more carbon atoms are optionally oxo-substituted and in which one or more carbon atoms are optionally replaced independently of one another by a nitrogen, oxygen or sulphur atom. Preferred examples which may be mentioned are methylene, ethylene, propylene, propane-1,2-diyl, propane-2,2-diyl, butane-1,3-diyl, butane-2,4-diyl, pentane-2,4-diyl, 2-methyl-pentane-2,4-diyl, -O-CH_2-, -S-CH_2-, -CH_2-O-, -CH_2-S-, -CH_2-O-CH_2-, -O-CH_2-CH_2-, 1-oxapropane-1,2-diyl, 3-oxabutane-2,4-diyl, 3-thiabutane-2,4-diyl, -O-$CH_2C(=O)$- and -O-CH_2-$CH_2C(=O)$-.

Alkoxy stands by way of example and preferably for methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino stands for an alkylamino radical having one or two alkyl substituents (chosen independently of one another), by way of example and preferably methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino.

Alkylaminocarbonyl stands for an alkylaminocarbonyl radical having one or two alkyl substituents (chosen independently of one another), by way of example and preferably methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-t-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylaminocarbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl.

Alkoxycarbonyl stands by way of example and preferably for methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Cycloalkyl stands for a cycloalkyl group having usually 3 to 8, preferably 5 to 7, carbon atoms, with cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl being mentioned by way of example and preferably for cycloalkyl.

Aryl stands for a mono- to tricyclic aromatic radical having usually 6 to 14 carbon atoms; phenyl, naphthyl and phenanthrenyl are mentioned by way of example and preferably for aryl.

Heteroaryl stands for an aromatic, mono- or bicyclic radical having usually 5 to 10, preferably 5 to 6, ring atoms and up to 5, preferably up to 4, heteroatoms from the series S, O and N, by way of example and preferably thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, oxadiazolyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Heterocyclyl stands for a mono- or polycyclic, preferably mono- or bicyclic, heterocyclic radical having usually 4 to 10, preferably 5 to 8, ring atoms and up to 3, preferably up to 2, heteroatoms and/or hetero groups from the series N, O, S, SO, SO_2. The heterocyclyl radicals may be saturated or partially unsaturated. 5- to 8-membered, monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the series O, N and S are preferred, such as by way of example and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

Heterocyclylcarbonyl stands for a heterocyclyl radical which is linked via a carbonyl group, such as by way of example and preferably tetrahydrofuran-2-ylcarbonyl, pyrrolidin-2-ylcarbonyl, pyrrolidin-3-ylcarbonyl, pyrrolinylcarbonyl, piperidinylcarbonyl, morpholinylcarbonyl, perhydroazepinylcarbonyl.

Halogen stands for fluorine, chlorine, bromine and iodine, preferably for fluorine and chlorine.

If radicals in the compounds according to the invention are substituted, the radicals may, unless specified otherwise, have one or more identical or different substituents. Substitution by up to three identical or different substituents is preferred. Substitution by one substituent is very particularly preferred.

In a further embodiment, the invention relates to compounds of the formula (I)

in which

Y is a C_1-C_6-alkylene chain which optionally contains one or more double or triple bonds, in which one or more carbon atoms are optionally oxo-substituted and in which one or more carbon atoms are optionally replaced independently of one another by a nitrogen, oxygen or sulphur atom, it being necessary for at least one carbon atom to be present between the heteroatom in Y and R^3, and it being necessary for at least one carbon atom to be present between two heteroatoms in Y,

R^1 is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl or alkylaminocarbonyl,

n is a number 0, 1, 2 or 3,

where if n is 2 or 3 the R^1 radicals may be identical or different,

R^2 is alkyl,

where alkyl may be substituted by 0, 1 or 2 substituents, where the substituents are selected independently of one another from the group consisting of halogen, hydroxyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, aryl, heteroaryl, cycloalkyl and heterocyclyl,

where aryl, heteroaryl, cycloalkyl and heterocyclyl may be substituted by 0, 1, 2 or 3 substituents, where the substituents are selected independently of one another from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^3 is hydroxyl or amino,

R^4 is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl or alkylaminocarbonyl,

and

m is a number 0, 1 or 2,

where if m is 2 the R^4 radicals may be identical or different.

In a further embodiment, the invention relates to compounds of the formula (I)

in which

Y is $-O-CH_2C(=O)-$ or $-O-(CH_2)_2C(=O)-$,

where Y is linked via the oxygen to the dibenzoxazepine ring,

R^1 is halogen, trifluoromethyl, cyano, amino, hydroxyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl or alkylaminocarbonyl,

where alkoxycarbonyl may be substituted by 0 or 1 substituent, where the substituent is selected from the group consisting of alkoxy, aryl, cycloalkyl and trimethylsilyl,

n is a number 1 or 2,

where if n is 2 the R^1 radicals may be identical or different,

R^2 is alkyl,

where alkyl may be substituted by 0 or 1 substituent, where the substituent is selected from the group consisting of hydroxyl, alkoxy, carboxyl, alkoxycarbonyl, aryl and heteroaryl,

where aryl and heteroaryl may be substituted by 0, 1, 2 or 3 substituents, where the substituents are selected independently of one another from the group consisting of halogen, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^3 is hydroxyl,

and

m is a number 0.

In a further embodiment, the invention relates to compounds of the formula (I)

in which

Y is $-O-CH_2C(=O)-$,

where Y is linked via the oxygen to the dibenzoxazepine ring,

R^1 is halogen, amino, hydroxyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl or alkylaminocarbonyl,

n is a number 0, 1 or 2,

where if n is 2 the R^1 radicals may be identical or different,

R^2 is alkyl,

where alkyl may be substituted by 0 or 1 substituent, where the substituent is selected from the group consisting of hydroxyl, alkoxy, carboxyl, alkoxycarbonyl, aryl and heteroaryl,

where aryl and heteroaryl may be substituted by 0, 1, 2 or 3 substituents, where the substituents are selected independently of one another from the group consisting of halogen, amino, alkylamino, hydroxyl, alkyl, alkoxy, carboxyl, alkoxycarbonyl, aminocarbonyl and alkylaminocarbonyl,

R^3 is hydroxyl,

and

m is a number 0.

In a further embodiment, the invention relates to compounds of the formula (I)

in which

Y is $-O-CH_2C(=O)-$,

where Y is linked via the oxygen in the ortho position to the amide function of the dibenzoxazepine ring,

R^1 is fluorine, chlorine, bromine, trifluoromethyl, cyano, carboxyl, methoxycarbonyl or ethoxycarbonyl,

where methoxycarbonyl and ethoxycarbonyl may be substituted by 0 or 1 substituent, where the substituent is selected from the group consisting of methoxy, phenyl, cyclopentyl and trimethylsilyl,

n is a number 1,

R^2 is alkyl,

where alkyl is substituted by 1 substituent, where the substituent is selected from the group consisting of hydroxyl, tert-butyloxy, tert-butyloxycarbonyl and 2,2-dimethylprop-1-yloxycarbonyl,

R^3 is hydroxyl,

and

m is a number 0.

Preferred compounds of the formula (I) for the purposes of the present invention are those in which

Y is $-O-CH_2C(=O)-$, where Y is linked via the oxygen to the dibenzoxazepine ring,

R^3 is hydroxyl,

and R^1, R^2, R^4, m and n are as defined above.

Preferred compounds of the formula (I) for the purposes of the present invention are those in which

Y is $-O-CH_2C(=O)-$, where Y is linked via the oxygen in the ortho position to the amide function of the dibenzoxazepine ring,

R^3 is hydroxyl,

and R^1, R^2, R^4, m and n are as defined above.

Preferred compounds of the formula (I) for the purposes of the present invention are also those in which

R^1 is alkoxycarbonyl,

and R^2 to R^4, Y, m and n are as defined above.

Preferred compounds of the formula (I) for the purposes of the present invention are also those in which

R^1 is trifluoromethyl, cyano, carboxyl or methoxycarbonyl,

and R^2 to R^4, Y, m and n are as defined above.

Preferred compounds of the formula (I) for the purposes of the present invention are also those in which

R^1 is trifluoromethyl or cyano,

and R^2 to R^4, Y, m and n are as defined above.

Preferred compounds of the formula (I) for the purposes of the present invention are also those in which

n is a number 1,

and R^1 to R^4, Y and m are as defined above.

Preferred compounds of the formula (I) for the purposes of the present invention are also those in which

R^2 is alkyl,

where alkyl may be substituted by 1 substituent, where the substituent is selected from the group consisting of carboxyl and alkoxycarbonyl,

and R^1, R^3, R^4, Y, m and n are as defined above.

Preferred compounds of the formula (I) for the purposes of the present invention are also those in which

R^2 is tert-butyloxycarbonylmethyl,

and R^1, R^3, R^4, Y, m and n are as defined above.

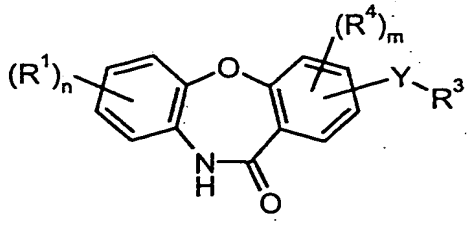
Preferred compounds of the formula (I) for the purposes of the present invention are also those in which

m is a number 0, i.e. no R^4 substituent is present,

and R^1 to R^3, Y and n are as defined above.

The invention further relates to processes for preparing the compounds of the formula (I), characterized in that

[A] compounds of the formula



(II),

in which R^1, R^3, R^4, Y, m and n have the meaning indicated above, are reacted with compounds of the formula

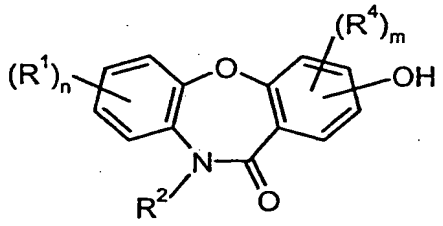
$$R^2—X^1 \quad (III),$$

in which R^2 has the meaning indicated above, and

X^1 is halogen, preferably chlorine or bromine,

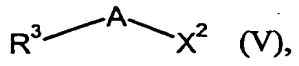
or

[B] compounds of the formula



(IV),

in which R^1, R^2, R^4, m and n have the meaning indicated above, are reacted with compounds of the formula



(V),

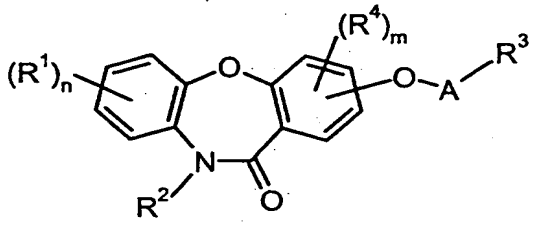
in which R^3 has the meaning indicated above,

X^2 is halogen, preferably chlorine or bromine, and

A is the C_1-C_6-alkylene chain of Y which has been shortened by a heavy atom and which optionally contains one or more double or triple bonds, in which one or more carbon atoms are optionally oxo-substituted and in which one or more carbon atoms are optionally replaced independently of one another by a

nitrogen, oxygen or sulphur atom, it being necessary for at least one carbon atom to be present between the heteroatom in A and R^3, and it being necessary for at least one carbon atom to be present between two heteroatoms in A,

to give compounds of the formula



(Ia),

in which R^1 to R^4, A, m and n have the meaning indicated above.

The compounds of the formula (Ia) are compounds of the formula (I), in which Y equals -O-A-.

Reaction by process [A] and process [B] generally takes place in inert solvents in the presence of a base, where appropriate in the presence of potassium iodide, preferably in a temperature range from room temperature to 50°C under atmospheric pressure.

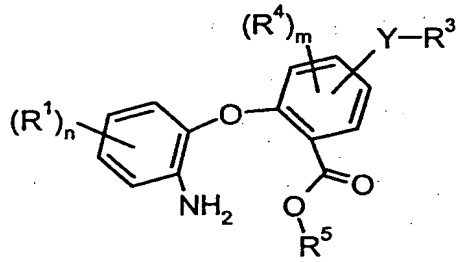
Examples of bases are alkali metal hydroxides such as sodium, lithium or potassium hydroxide, or alkali metal carbonates, such as caesium carbonate, sodium or potassium carbonate, where appropriate in aqueous solution, with preference for potassium carbonate.

Examples of inert solvents are ethers, such as 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, or dimethylformamide, or mixtures of solvents, with preference for dimethylformamide or dioxane.

The radicals R^1, R^2 and R^3 in the compounds of the formula (I) may, where appropriate, contain protective groups which, after the reaction, are eliminated by a deprotection reaction. This takes place by standard processes of protective group chemistry.

The compounds of the formulae (III) and (V) are known or can be synthesized by known processes from the appropriate precursors.

The compounds of the formula (II) are known or can be prepared by reacting compounds of the formula



(VI),

in which R^1, R^3, R^4, Y, m and n have the meaning indicated above, and

R^5 is alkyl, preferably methyl or ethyl,

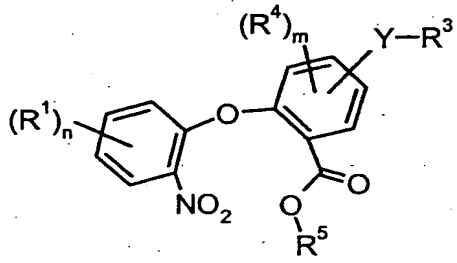
with acidic organic catalysts.

The reaction generally takes place in inert solvents, preferably in a temperature range from 50°C to the reflux of the solvent under atmospheric pressure.

Examples of acidic organic catalystics are para-toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid or camphorsulphonic acid, with preference for p-toluenesulphonic acid.

Examples of inert solvents are ethers such as dioxane, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene, toluene or petroleum fractions, with preference for xylene or toluene.

The compounds of the formula (VI) are known or can be prepared by reacting compounds of the formula



(VII),

in which R^1, R^3, R^4, R^5, Y, m and n have the meaning indicated above,
with a reducing agent.

The reaction generally takes place in inert solvents, preferably in a temperature range from room temperature to the reflux of the solvent under atmospheric pressure up to 3 bar.

Examples of reducing agents are palladium on carbon in a hydrogen atmosphere, palladium on carbon in the presence of ammonium formate, iron in concentrated acetic acid, iron/iron(III) chloride, tin(II) chloride or tin in hydrochloric acid, with preference for tin(II) chloride.

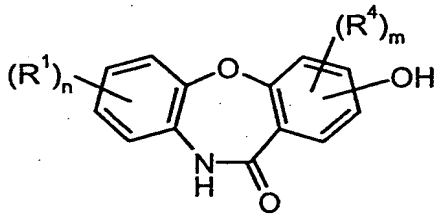
Examples of inert solvents are ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, or mixtures of alcohols with water, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other

solvents such as dimethylformamide, dimethylacetamide, acetonitrile, ethyl acetate or pyridine.

Preference is given in the case of palladium on carbon to ethanol, methanol, isopropanol, tetrahydrofuran or a mixture of ethyl acetate and ethanol, in the case of iron/iron(III) chloride to a mixture of water and ethanol and in the case of tin(II) chloride to dimethylformamide, dioxane or methanol.

The compounds of the formula (VII) are known or can be synthesized by known processes from the appropriate precursors.

The compounds of the formula (IV) are known or can be prepared by reacting compounds of the formula



(VIII),

in which R^1, R^4, m and n have the meaning indicated above, with compounds of the formula

$$R^2—X^3 \quad (IX),$$

in which R^3 has the meaning indicated above, and

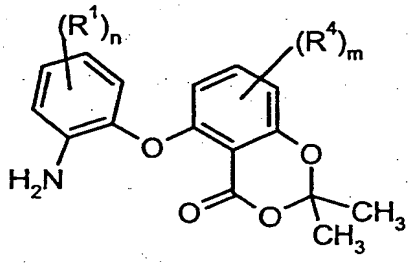
X^3 is halogen, preferably chlorine or bromine,

with one equivalent of the compounds of the formula (IX).

The reaction takes place under the reaction conditions described for processes [A] and [B].

The compounds of the formula (IX) are known or can be synthesized by known processes from the appropriate precursors.

The compounds of the formula (VIII) are known or can be prepared by reacting compounds of the formula

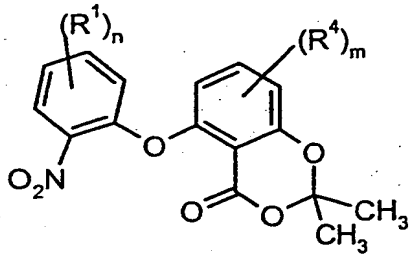


(X),

in which R^1, R^4, m and n have the meaning indicated above, with weak acids.

The reaction takes place under the reaction conditions described for compounds of the formula (II).

The compounds of the formula (X) are known or can be prepared by reacting compounds of the formula



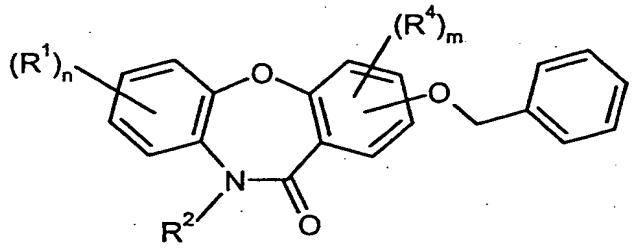
(XI),

in which R^1, R^4, m and n have the meaning indicated above, with a reducing agent.

The reaction takes place under the reaction conditions described for compounds of the formula (VI).

The compounds of the formula (XI) are known or can be synthesized by known processes from the appropriate precursors.

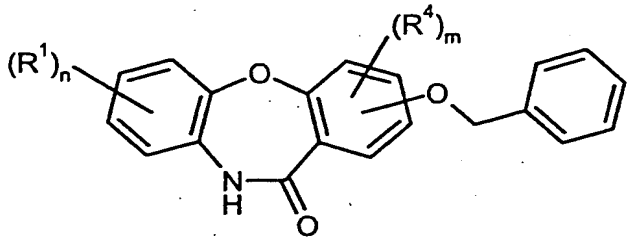
In an alternative process, compounds of the formula (IV) can be prepared by reacting compounds of the formula



(XII),

in which R^1, R^2, R^4, m and n have the meaning indicated above, with reducing agents, with preference for reaction with palladium on carbon in a hydrogen atmosphere in ethanol, methanol, isopropanol or tetrahydrofuran in a temperature range from room temperature to the reflux of the solvent under atmospheric pressure up to 3 bar.

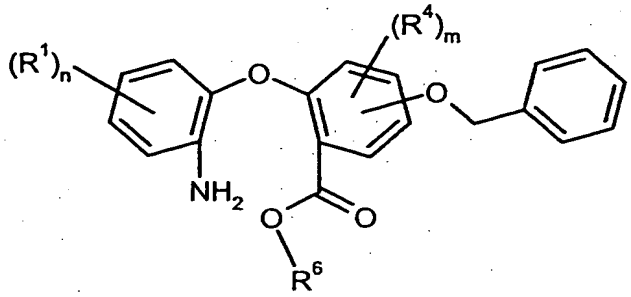
The compounds of the formula (XII) are known or can be prepared by reacting compounds of the formula



(XIII),

in which R^1, R^4, m and n have the meaning indicated above, with compounds of the formula (III) under the reaction conditions described for process [A].

The compounds of the formula (XIII) are known or can be prepared by reacting compounds of the formula



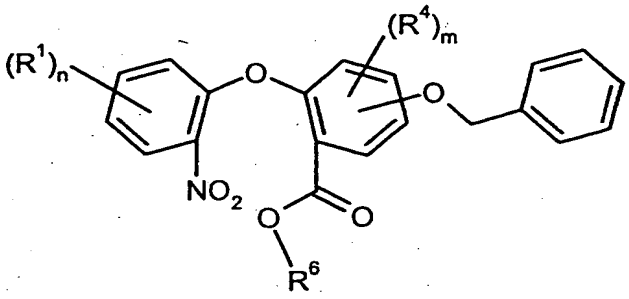
(XIV),

in which R^1, R^4, m and n have the meaning indicated above, and

R^6 is alkyl, preferably methyl or ethyl,

under the reaction conditions described for compounds of the formula (II).

The compounds of the formula (XIV) are known or can be prepared by reacting compounds of the formula



(XV),

in which R^1, R^4, R^6, m and n have the meaning indicated above, under the reaction conditions described for compounds of the formula (VI).

The compounds of the formula (XV) are known or can be synthesized by known processes from the appropriate precursors.

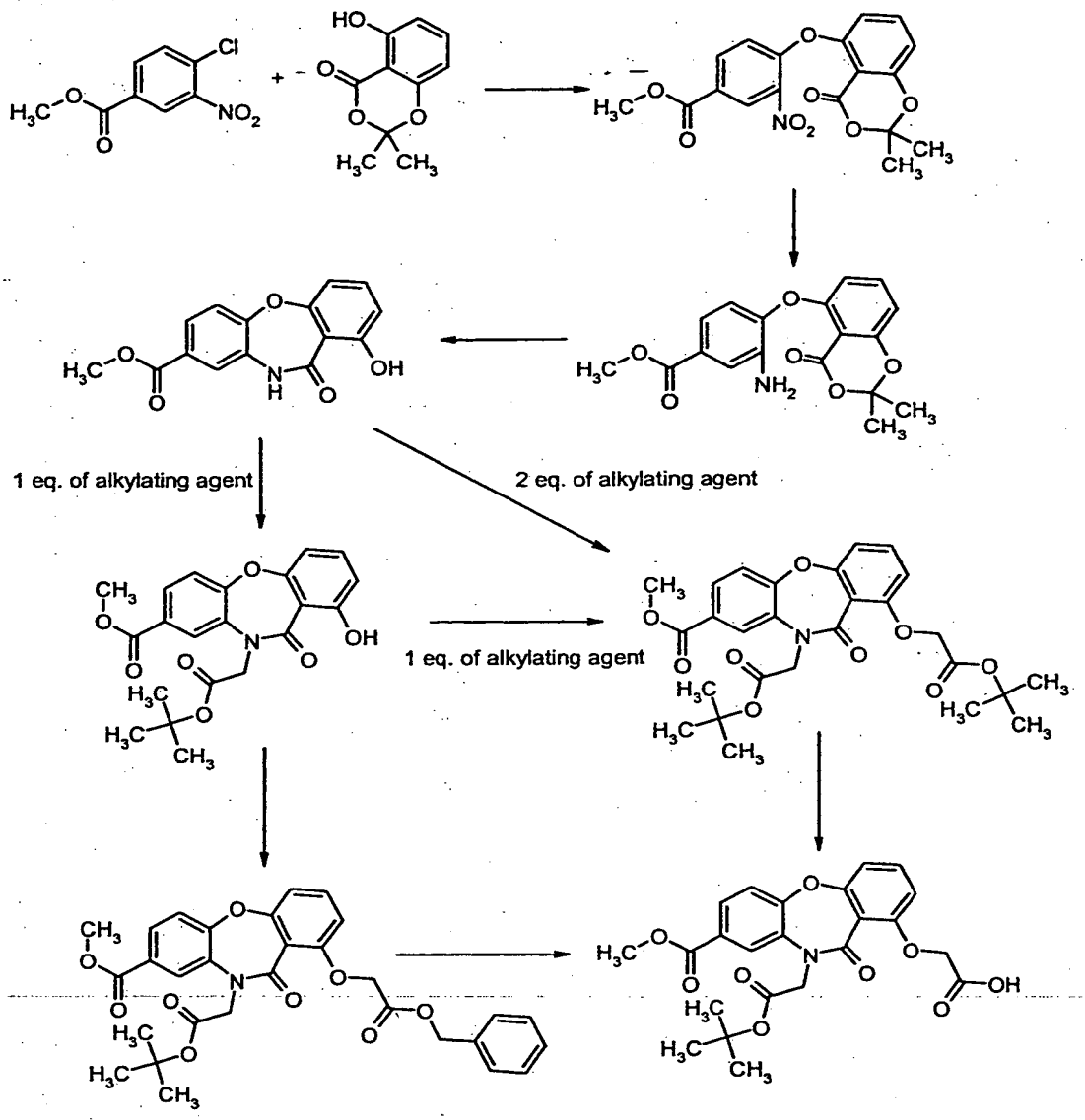
In the case where R^2 is tert-butoxycarbonylmethyl, the reaction can take place by the following alternative process:

1) Reaction of compounds of the formula (VIII) with two equivalents of tert-butyl bromoacetate under the reaction conditions described for process [A] (compare Example 55A).

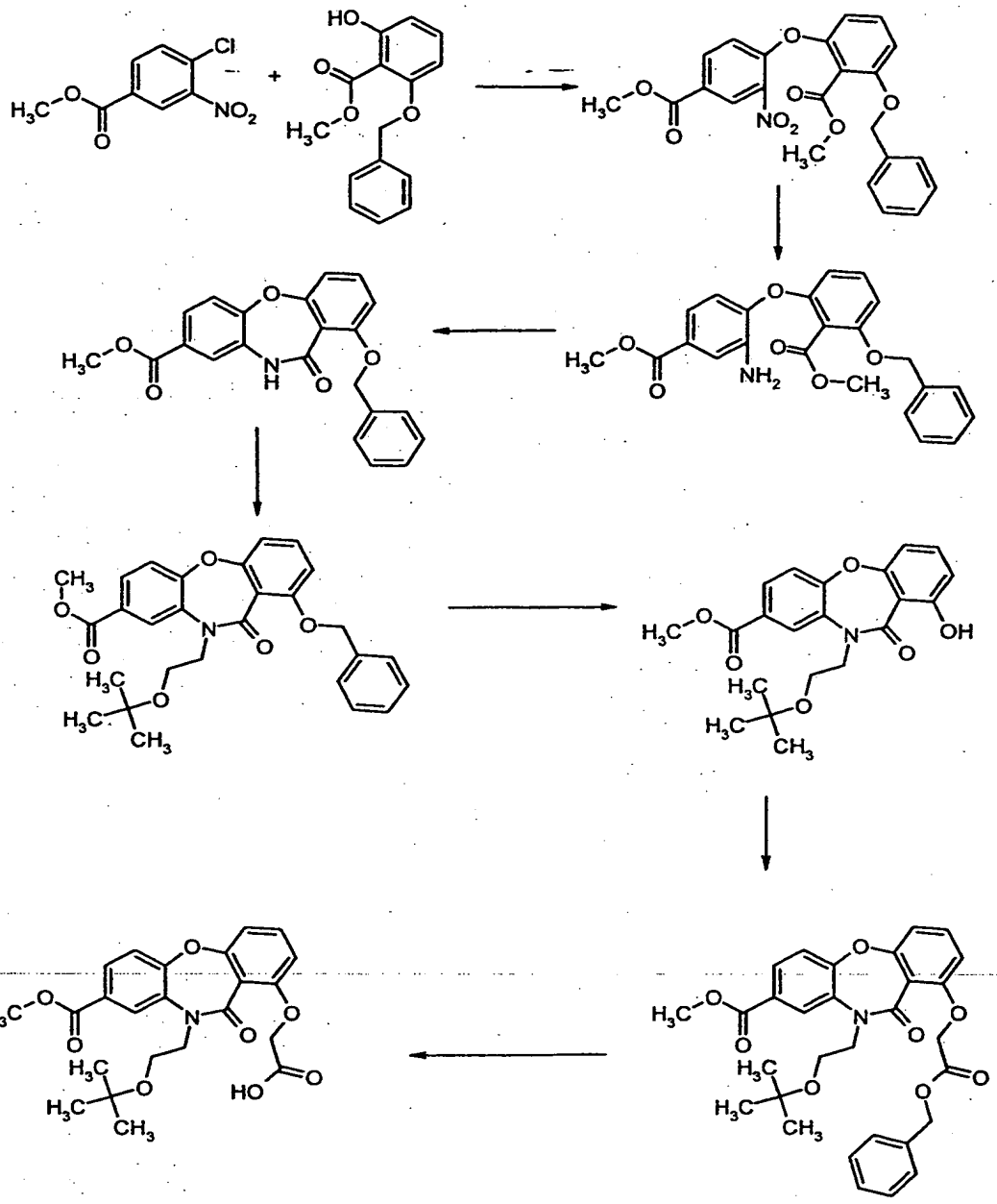
2) Selective elimination of the tert-butyl group on $-Y-R^3$ by reaction with chlorotrimethylsilane and sodium iodide in trichloromethane (compare Example 12).

The preparation of the compounds according to the invention can be illustrated by the following synthesis schemes:

Scheme 1:


1 eq. of alkylating agent
2 eq. of alkylating agent
1 eq. of alkylating agent

Scheme 2:



The present invention further relates to compounds of the formula (I) for controlling disorders, especially cardiovascular disorders, e.g. atherosclerosis, and to medicaments comprising compounds of the formula (I) and excipients and also to the use of compounds of the formula (I) for producing a medicament for the treatment of cardiovascular disorders, especially atherosclerosis.

They can be employed for the prevention and treatment of cardiovascular disorders (such as, for example, atherosclerosis, reperfusion tissue damage after stroke, myocardial infarction or peripheral vascular occlusions) or inflammatory disorders and autoimmune diseases (such as, for example, arthritis, rheumatoid arthritis, osteoporosis, Crohn's disease, chronic inflammatory lung diseases such as adult respiratory distress syndrome (ARDS), transplant rejections, chronic inflammatory fibrotic changes in organs, such as hepatic fibrosis, or the generalized autoimmune disease systemic lupus erythematosus or other forms of lupus erythematosus or dermal inflammatory diseases such as psoriasis) or cancers (such as, for example, lung cancer and prostate cancer) or chronic pain.

The active ingredient may act systemically and/or locally. For this purpose, it can be administered in a suitable way, such as, for example, by the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, transdermal, conjunctival or otic route or as implant.

The active ingredient can be administered in administration forms suitable for these administration routes.

Suitable for oral administration are known administration forms which deliver the active ingredient rapidly and/or in a modified manner, such as, for example, tablets (uncoated and coated tablets, e.g. tablets provided with enteric coatings or film-coated tablets), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions and solutions.

Parenteral administration can take place with avoidance of an absorption step (intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with inclusion of an absorption (intramuscular, subcutaneous, intracutaneous, percutaneous, or intraperitoneal). Administration forms suitable for parenteral administration are, inter

alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

Oral administration is preferred.

Suitable for other administration routes are, for example, pharmaceutical forms for inhalation (including powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets or capsules for lingual, sublingual or buccal administration, suppositories, preparations for the ears and eyes, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milk, pastes, dusting powders or implants.

The active ingredients can be converted into the stated administration forms in a manner known per se. This takes place with use of inert, non-toxic, pharmaceutically suitable excipients. These include, inter alia, carriers (e.g. microcrystalline cellulose), solvents (e.g. liquid polyethylene glycols), emulsifiers (e.g. sodium dodecyl sulphate), dispersants (e.g. polyvinylpyrrolidone), synthetic and natural biopolymers (e.g. albumin), stabilizers (e.g. antioxidants such as ascorbic acid), colourings (for example inorganic pigments such as iron oxides) or masking flavours and/or odours.

It has generally proved to be advantageous on parenteral administration to administer amounts of about 5 to 250 mg/kg of body weight every 24 hours to achieve effective results. The amount on oral administration is about 5 to 100 mg/kg of body weight every 24 hours.

It may nevertheless be necessary to deviate from the amounts mentioned, in particular depending on the body weight, administration route, individual response to the active ingredient, mode of preparation and time or interval over which administration takes place.

The percentage data in the following tests and examples are percentages by weight unless indicated otherwise; parts are parts by weight. Solvent ratios, dilution ratios and concentration data for liquid/liquid solutions are in each case based on volume. The statement "w/v" means "weight/volume". Thus, for example, "10% w/v" means: 100 ml of solution or suspension contain 10 g of substance.

A) **Examples**

Abbreviations:

Boc	tert-butoxycarbonyl
BSA	basal medium
$CDCl_3$	deuterochloroform
conc.	concentrated
CO_2	carbon dioxide
DIEA	*N,N*-diisopropylethylamine
DMAP	4-*N,N*-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
EDCI	*N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide x HCl
eq.	equivalent
ESI	electrospray ionization (in MS)
h	hour
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HPLC	high pressure, high performance liquid chromatography
LC-MS	coupled liquid chromatography/mass spectroscopy
min	minute(s)
MOPS	3-morpholinopropanesulphonic acid
MPLC	medium pressure liquid chromatography
MS	mass spectroscopy
MW	molecular weight [g/mol]
NMR	nuclear magnetic resonance spectroscopy
Pd/C	palladium/carbon
R_f	retention index (in TLC)
RP	reverse phase
RP-HPLC	reverse phase HPLC

RT	room temperature
R_t	retention time (in HPLC)
sat.	saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tris	Tris(hydroxymethyl)methylamine
Tris-HCl	Tris(hydroxymethyl)methylamine hydrochloride

HPLC and LC-MS methods:

Method 1 (HPLC): column C18, 2.1x150 mm, temperature 50°C, eluent A: acetonitrile, eluent B: 0.1% hydrochloric acid in water, gradient: 0-3 min A:B = 10:90, flow rate 0.9 ml/min; 3-6 min A:B = 90:10, flow rate 1.2 ml/min.

Method 2 (LC-MS): Instrument: Micromass Platform LCZ with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l of water + 1 ml of 50% strength formic acid, eluent B: 1 l of acetonitrile + 1 ml of 50% strength formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

Method 3 (LC-MS): Instrument: Micromass Platform LCZ with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l of water + 1 ml of 50% strength formic acid, eluent B: 1 l of acetonitrile + 1 ml of 50% strength formic acid ; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

Method 4 (LC-MS): Instrument: Micromass Quattro LCZ with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A:

1 l of water + 1 ml of 50% strength formic acid, eluent B: 1 l of acetonitrile + 1 ml of 50% strength formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

Method 5 (LC-MS): MS apparatus type: Micromass ZQ; HPLC apparatus type: Waters Alliance 2790; column: Grom-Sil 120 ODS-4 HE 50x2 mm, 3.0 µm; eluent A: water + 500 µl of 50% strength formic acid / l; eluent B: acetonitrile + 500 µl of 50% strength formic acid / l; gradient: 0.0 min 0%B→ 0.2 min 0%B→ 2.9 min 70%B→ 3.1 min 90%B→ 4.5 min 90%B; oven: 45°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 6 (LC-MS): MS apparatus type: Micromass ZQ; HPLC apparatus type: HP 1100 series; UV DAD; column: Grom-Sil 120 ODS-4 HE 50x2 mm, 3.0 µm; eluent A: water + 500 µl of 50% strength formic acid / l, eluent B: acetonitrile + 500 µl of 50% strength formic acid / l; gradient: 0.0 min 70%B → 4.5 min 90%B; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 7 (LC-MS): MS apparatus type : Micromass ZQ; HPLC apparatus type: HP 1100 series; UV DAD; column: Grom-Sil 120 ODS-4 HE 50x2 mm, 3.0 µm; eluent A: water + 500 µl of 50% strength formic acid / l, eluent B: acetonitrile + 500 µl of 50% strength formic acid / l; gradient: 0.0 min 0%B → 2.9 min 70%B → 3.1 min 90%B → 4.5 min 90%B; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 8 (HPLC): Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm x 2 mm, 3.5 µm; eluent A: 5 ml of $HClO_4$/l of water, eluent B: acetonitrile; gradient: 0 min 2%B, 0.5 min 2%B, 4.5 min 90%B, 6.5 min 90%B; flow rate: 0.75 ml/min; temp.: 30°C; UV detection: 210 nm.

Method 9 (HPLC): Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm x 2 mm, 3.5 µm; eluent A: 5 ml of $HClO_4$/l of water, eluent B:

acetonitrile; gradient: 0 min 2%B, 0.5 min 2%B, 4.5 min 90%B, 9 min 90%B; flow rate: 0.75 ml/min; temp.: 30°C, UV detection: 210 nm.

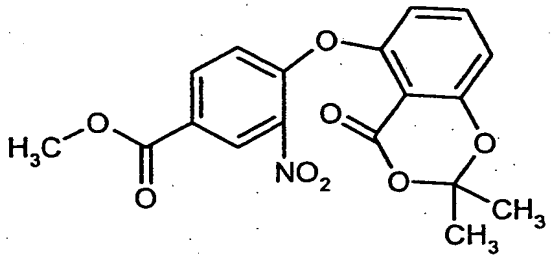
Method 10 (LC-MS): MS apparatus type: Micromass ZQ; HPLC apparatus type: Waters Alliance 2795; column: Merck Chromolith SpeedROD RP-18e 50x4.6 mm; eluent A: water + 500 µl of 50% strength formic acid / l; eluent B: acetonitrile + 500 µl of 50% strength formic acid / l; gradient: 0.0 min 10%B→ 3.0 min 95%B→ 4.0 min 95%B; oven: 35°C; flow rate: 0.0 min 1.0 ml/min→ 3.0 min 3.0 ml/min→ 4.0 min 3.0 ml/min; UV detection: 210 nm.

Method 11 (preparative HPLC):
Column material: YMC GEL ODS AQ S 5/15 µm; mobile phase: acetonitrile/water gradient 10:90 -> 90:10.

Starting compounds:

Example 1A

Methyl 4-[(2,2-dimethyl-4-oxo-4H-1,3-benzodioxin-5-yl)oxy]-3-nitrobenzoate



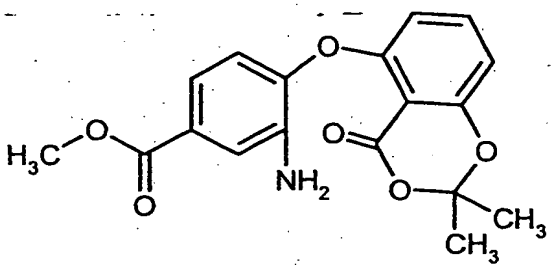
A solution of 7.59 g (35.2 mmol) of methyl 4-chloro-3-nitrobenzoate and 6.84 g (35.2 mmol) of 5-hydroxy-2,2-dimethyl-4H-1,3-benzodioxin-4-one (cf. A. Hadfield et al., Synth. Commun. **1994**, *24*, 1025) in dimethylformamide is mixed with 5.35 g (38.8 mmol) of potassium carbonate and stirred at 70°C for 8 h. The mixture is poured into 400 ml of ice-water and 250 ml of ethyl acetate. The organic phase is extracted with 150 ml each of water and saturated sodium chloride solution. The organic phases are dried over magnesium sulphate, and then the solvent is removed under reduced pressure. The residue is purified on a silica gel column (cyclohexane:ethyl acetate 2:1) to give 11.3 g (86% of theory) of product.

MS (DCI): m/z = 391 $(M+NH_4)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.67 (s, 9H), 3.88 (s, 3H), 7.04-7.1 (m, 3H), 7.81 (dd, 1H), 8.11 (dd, 1H), 8.54 (d, 1H).

Example 2A

Methyl 3-amino-4-[(2,2-dimethyl-4-oxo-4H-1,3-benzodioxin-5-yl)oxy]benzoate



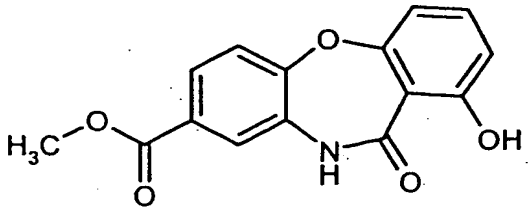
10.9 g (29.1 mmol) of the compound from Example 1A in 116 ml of conc. acetic acid and 6 ml of water are mixed with 11.4 g (204 mmol) of iron and stirred at 50°C for 3 h. The mixture is poured into 580 ml of acetone, and the solid is filtered off. The filtrate is purified on a silica gel column (dichloromethane:ethyl acetate 100:5) to give 9.93 g (95% of theory) of product.

MS (DCI): m/z = 361 $(M+NH_4)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6):δ = 1.71 (s, 9H), 3.81 (s, 3H), 5.31 (s, 2H), 6.53 (d, 1H), 6.85 (dd, 2H), 7.16 (dd, 1H), 7.46 (d, 1H), 7.56 (dd, 1H).

Example 3A

Methyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



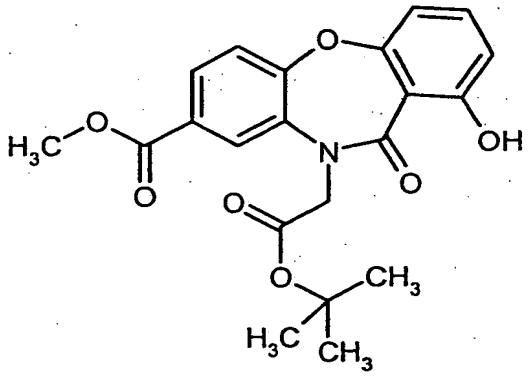
9.87 g (28.8 mmol) of the compound from Example 2A in 140 ml of xylene are mixed with 0.55 mg (2.9 mmol) of para-toluenesulphonic acid and stirred under reflux overnight. Methanol washing of the crystals which have separated out results in 6.96 g (84% of theory) of product.

MS (ESI): m/z = 286 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.85 (s, 3H), 6.80-6.90 (m, 2H), 7.45-7.54 (m, 2H), 7.77 (dd, 1H), 7.84 (d, 1H).

Example 4A

Methyl 10-(2-tert-butoxy-2-oxoethyl)-1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f]-[1,4]oxazepine-8-carboxylate



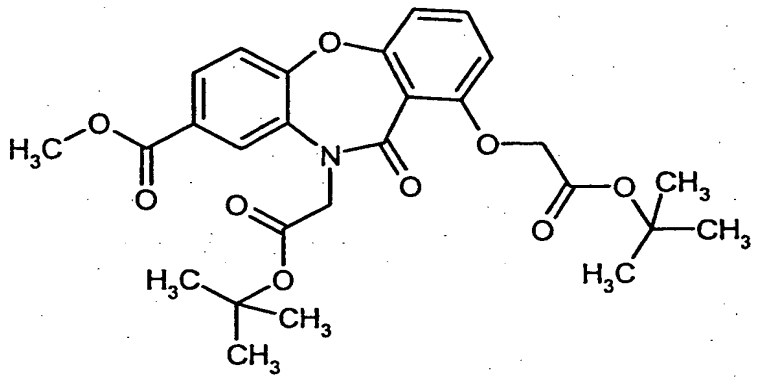
300 mg (1.05 mmol) of the compound from Example 3A in 3 ml of dimethylformamide are mixed with 205 mg (1.05 mmol) of tert-butyl bromoacetate and 145 mg (1.05 mmol) of potassium carbonate and stirred at room temperature overnight. The mixture is poured into 20 ml of water and 20 ml of ethyl acetate. The organic phase is extracted with 20 ml each of water and saturated sodium chloride solution. The organic phases are dried over magnesium sulphate. Removal of the solvent under reduced pressure results in a residue which is purified on a silica gel column (dichloromethane) to give 213 mg (51% of theory) of product.

MS (ESI): m/z = 422 $(M+Na)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.44 (s, 9H), 3.85 (s, 3H), 4.70 (s, 2H), 6.82 (d, 1H), 6.90 (d, 1H), 7.43 (dd, 1H), 7.53 (d, 1H), 7.85 (d, 1H), 7.91 (s, 1H), 10.44 (s, 1H).

Example 5A

Methyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



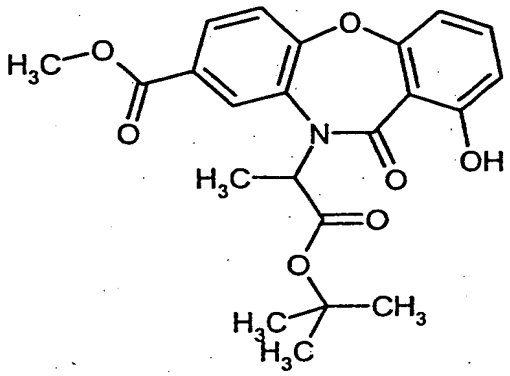
95 mg (0.24 mmol) of the compound from Example 4A in 3 ml of dimethylformamide are mixed with 46 mg (0.24 mmol) of tert-butyl bromoacetate and 49 mg (0.35 mmol) of potassium carbonate and stirred at room temperature overnight. The mixture is poured into 20 ml of water and 20 ml of ethyl acetate. The organic phase is extracted with 20 ml each of water and saturated sodium chloride solution. The organic phase is dried over magnesium sulphate. Removal of the solvent under reduced pressure results in 0.12 g (99% of theory) of product.

MS (DCI): m/z = 531 $(M+NH_4)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.34 (s, 9H), 1.39 (s, 9H), 3.84 (s, 3H), 4.64-4.72 (m, 4H), 6.82 (d, 1H), 7.01 (d, 1H), 7.40-7.54 (m, 2H), 7.81 (dd, 1H), 7.96 (d, 1H).

Example 6A

Methyl (R,S)-10-(2-tert-butoxy-1-methyl-2-oxoethyl)-1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate

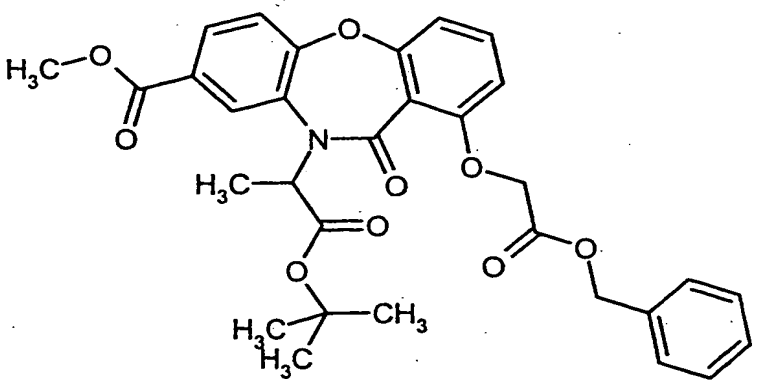


Preparation takes place in analogy to Example 4A from 400 mg (1.4 mmol) of the compound from Example 3A and 293 mg (1.4 mmol) of tert-butyl (R,S)-bromopropionate. Purification takes place on a silica gel column (ethyl acetate:cyclohexane 5:1) to give 37 mg (7% of theory) of product.

LC-MS (method 2): R_t = 4.2 min,
MS (ESI): m/z = 436 $(M+Na)^+$

Example 7A

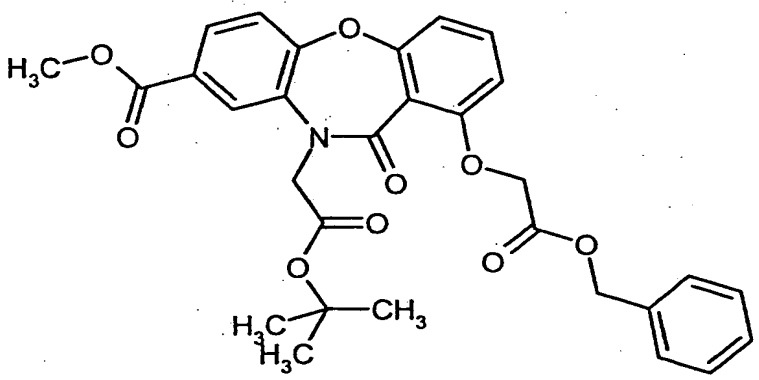
Methyl (R,S)-1-[2-(benzyloxy)-2-oxoethoxy]-10-(2-tert-butoxy-1-methyl-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



37 mg (0.089 mmol) of the compound from Example 6A are dissolved in 1 ml of DMF and mixed with 18.5 mg (0.13 mmol) of potassium carbonate and 20.5 mg (0.089 mmol) of benzyl bromoacetate. The mixture is stirred at RT for 4 h and, after addition of 5 ml of water, extracted with ethyl acetate. The combined organic phases are dried over magnesium sulphate and concentrated in vacuo. 18 mg (36% of theory) of the prodct are obtained and are reacted without further purification.

Example 8A

Methyl 1-[2-(benzyloxy)-2-oxoethoxy]-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



Preparation takes place in analogy to Example 7A from 2 g (5.0 mmol) of the compound from Example 4A and 1.15 g (5.0 mmol) of benzyl bromoacetate. Purification by chromatography on a silica gel column (dichloromethane:methanol 1:0 to 3:1) results in 2.47 g (90% of theory) of the product.

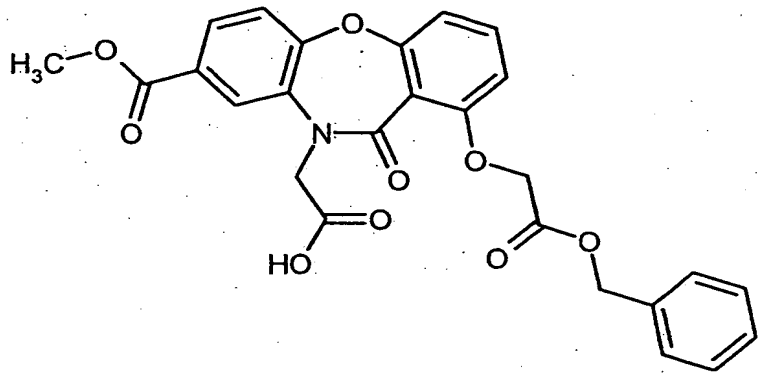
LC-MS (method 3): $R_t = 4.22$ min,

MS (ESI): m/z = 548 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.38 (s, 9H), 3.81 (s, 3H), 4.68 (d, 2H), 4.90 (d, 2H), 5.15 (s, 2H), 6.88 (d, 1H), 7.03 (d, 1H), 7.30 (s, 5H), 7.45 (dd, 1H), 7.52 (d, 1H), 7.82 (d, 1H), 7.95 (s, 1H).

Example 9A

[1-[2-(Benzyloxy)-2-oxoethoxy]-8-(methoxycarbonyl)-11-oxodibenzo[b,f][1,4]-oxazepin-10(11*H*)-yl]acetic acid



A solution of 500 mg (0.91 mmol) of the compound from Example 8A in 4 ml of dichloromethane is mixed with 0.35 ml (4.6 mmol) of trifluoroacetic acid. The mixture is stirred at RT for 16 h and then a further 0.35 ml (4.6 mmol) of trifluoroacetic acid is added. The mixture is stirred at RT for a further 5 h, diluted with ethyl acetate and washed several times with dilute hydrochloric acid. After drying over magnesium sulphate, the volatile constituents are condensed out in vacuo. The residue is purifed by preparative HPLC (method 11). 240 mg (53% of theory) of the desired product are obtained.

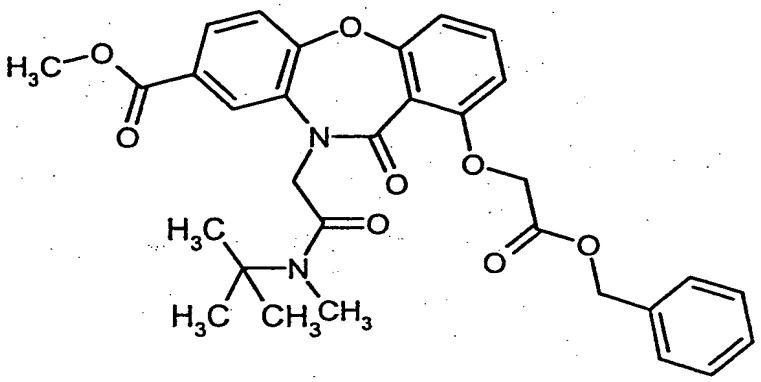
LC-MS (method 3): R_t = 3.49 min,

MS (ESI): m/z = 492 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3H), 4.62 (d, 1H), 4.76 (d, 1H), 4.91 (s, 2H), 5.15 (s, 2H), 6.87 (d, 1H), 7.03 (d, 1H), 7.30 (s, 5H), 7.46 (dd, 1H), 7.50 (d, 1H), 7.82 (d, 1H), 7.97 (s, 1H).

Example 10A

Methyl 1-[2-(benzyloxy)-2-oxoethoxy]-10-{2-[tert-butyl(methyl)amino]-2-oxoethyl}-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



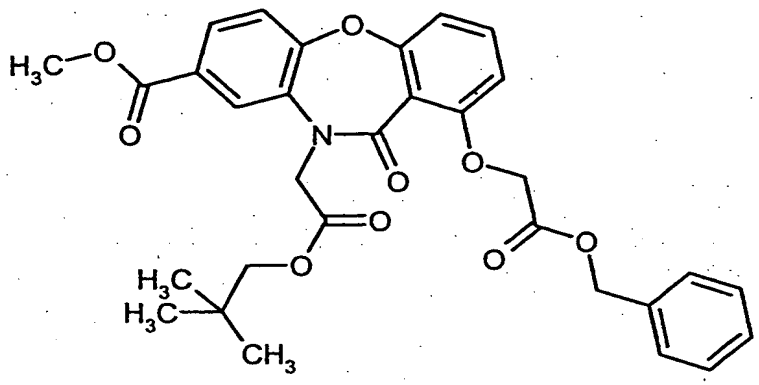
A solution of 50 mg (0.1 mmol) of the compound from Example 9A, 10.6 mg (0.12 mmol) of N-methyl-N-tert-butylamine and 77 mg (0.2 mmol) of HATU in 2 ml of DMF is mixed with 0.04 ml (0.2 mmol) of N,N-diisopropylethylamine. The mixture is stirred at RT for 16 h, diluted with ethyl acetate and washed successively with 0.1 M hydrochloric acid and sat. aqueous sodium bicarbonate solution. After drying over magnesium sulphate, the volatile constituents are removed in vacuo. The product is obtained and is reacted further without purification.

LC-MS (method 3): R_t = 3.88 min,

MS (ESI): m/z = 461 $(M+H)^+$.

Example 11A

Methyl 1-(2-benzyloxy-2-oxoethoxy)-10-(2-(2,2-dimethylpropoxy)-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



A solution of 50 mg (0.1 mmol) of the compound from Example 9A, 6.2 mg of DMAP and 29 mg (0.15 mmol) of EDCI in 6 ml of dichlormethane is mixed with 10.7 mg (0.12 mmol) of neopentyl alcohol. The mixture is stirred at RT for 16 h, diluted with ethyl acetate and washed successively with 0.1 M hydrochloric acid and sat. aqueous sodium bicarbonate solution. After drying over magnesium sulphate, the volatile constituents are removed in vacuo. 55 mg (98% of theory) of the product are obtained.

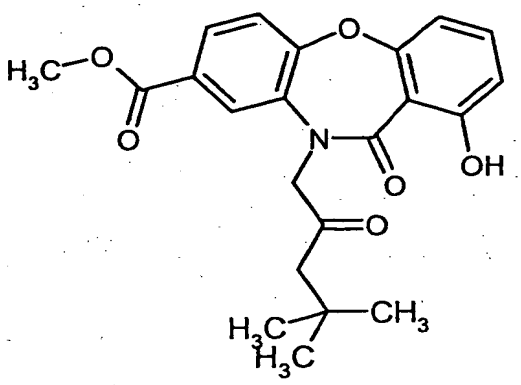
LC-MS (method 3): R_t = 4.06 min,

MS (ESI): m/z = 562 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.38 (s, 9H), 3.52 (s, 2H), 3.83 (s, 3H), 4.70 (d, 2H), 4.90 (s, 2H), 5.16 (s, 2H), 6.86 (d, 1H), 7.02 (d, 1H), 7.31 (s, 5H), 7.42 (dd, 1H), 7.52 (d, 1H), 7.82 (d, 1H), 8.00 (s, 1H).

Example 12A

Methyl 10-(4,4-dimethyl-2-oxopentyl)-1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f]-[1,4]oxazepine-8-carboxylate



Preparation takes place in analogy to Example 4A from 500 mg (1.75 mmol) of the compound from Example 3A and 338 mg (1.75 mmol) of 1-bromo-4,4-dimethyl-2-pentanone. Purification takes place on a silica gel column (ethyl acetate:cyclohexane 5:1) to give 290 mg (41% of theory) of the product.

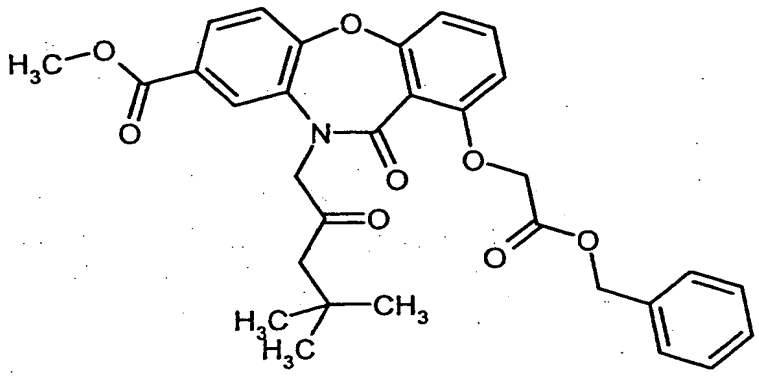
LC-MS (method 3): R_t = 4.60 min,

MS (ESI): m/z = 398 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.03 (s, 9H), 1.40 (s, 2H), 3.83 (s, 3H), 4.91 (s, 2H), 6.82 (d, 1H), 6.90 (d, 1H), 7.45 (dd, 1H), 7.51 (d, 1H), 7.68 (s, 1H), 7.83 (d, 1H).

Example 13A

Methyl 1-(2-benzyloxy-2-oxoethoxy)-10-(4,4-dimethyl-2-oxopentyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



Preparation takes place in analogy to Example 7A from 230 mg (0.58 mmol) of the compound from Example 12A and 133 mg (0.58 mmol) of benzyl bromoacetate. Purification by chromatography on a silica gel column (dichloromethane:methanol 1:0 to 3:1) results in 302 mg (91% of theory) of the product.

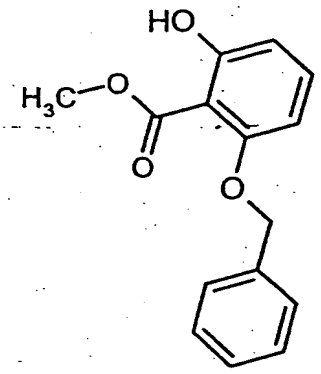
LC-MS (method 3): R_t = 4.04 min,

MS (ESI): m/z = 546 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.02 (s, 9H), 2.37 (d, 1H), 2.52 (d, 1H), 3.81 (s, 3H), 4.76 (d, 1H), 4.89 (s, 2H), 4.99 (d, 1H), 5.16 (s, 2H), 6.87 (d, 1H), 7.03 (d, 1H), 7.30 (s, 5H), 7.45 (dd, 1H), 7.51 (d, 1H), 7.77 (s, 1H), 7.79 (d, 1H).

Example 14A

Methyl 2-benzyloxy-6-hydroxybenzoate



4.8 ml (40.4 mmol) of benzyl bromide and 7.97 g (57.7 mmol) of potassium carbonate are successively added to a solution of 10 g (57.7 mmol) of methyl 2,6-dihydroxybenzoate in 100 ml of acetone. The mixture is stirred at RT overnight and, after addition of 500 ml of ethyl acetate, is washed with water and dried over magnesium sulphate, and the volatile constituents are removed in vacuo. The residue is taken up in 50 ml of acetone and again mixed with 2.4 ml of benzyl bromide and 4 g of potassium carbonate. Stirring overnight is repeated, and the mixture is worked up as described above. The resulting mixture is separated on a silica gel column (ethyl acetate:cyclohexane 1:5). 3.93 g (26% of theory) of the desired product are obtained.

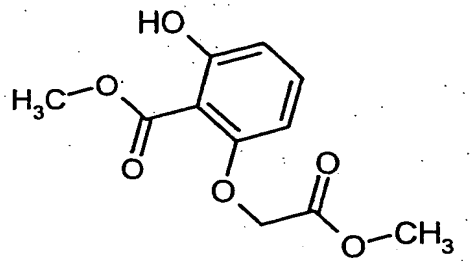
LC-MS (method 3): R_t = 3.47 min,

MS (ESI): m/z = 259 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.75 (s, 3H), 5.12 (s, 2H), 6.50 (d, 1H), 6.58 (d, 1H), 7.17 (dd, 1H), 7.35 (m, 5H), 9.98 (s, 1H).

Example 15A

Methyl 2-hydroxy-6-(2-methoxy-2-oxoethoxy)benzoate



Preparation takes place in analogy to Example 14A from 15 g (89.2 mmol) of methyl 2,6-dihydroxybenzoate, 12.3 g (80.3 mmol) of methyl bromoacetate, 12.3 g (89.2 mmol) of potassium carbonate in 120 ml of acetone. The resulting mixture is separated on a silica gel column (ethyl acetate:cyclohexane 1:5). 3.38 g (16% of theory) of the desired product are obtained.

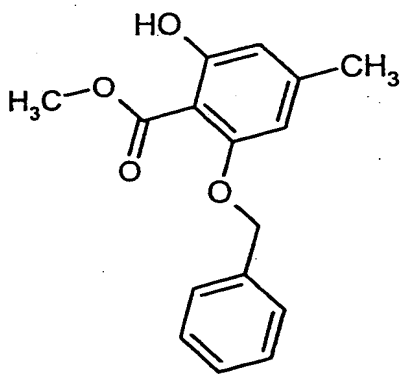
LC-MS (method 4): $R_t = 3.73$ min,

MS (ESI): m/z = 241 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.68 (s, 3H), 3.76 (s, 3H), 4.75 (s, 2H), 6.38 (d, 1H), 6.52 (d, 1H), 7.15 (dd, 1H), 10.00 (s, 1H).

Example 16A

Methyl 2-(benzyloxy)-6-hydroxy-4-methylbenzoate



Preparation takes place in analogy to Example 14A from 11 g (58.6 mmol) of methyl 2,6-dihydroxy-4-methylbenzoate and 9.02 g (52.7 mmol) of benzyl bromide. The resulting mixture is separated on a silica gel column (ethyl acetate:cyclohexane 1:5). 4.4 g (28% of theory) of the desired product are obtained.

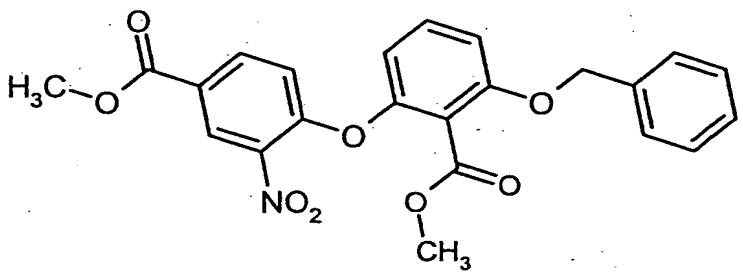
LC-MS (method 5): R_t = 3.72 min,

MS (ESI): m/z = 273 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 2.22 (s, 3H), 3.73 (s, 3H), 5.09 (s, 2H), 6.33 (s, 1H), 6.44 (s, 1H), 7.31 (m, 1H), 7.39 (m, 4H), 9.98 (s, 1H).

Example 17A

Methyl 4-[3-(benzyloxy)-2-(methoxycarbonyl)phenoxy]-3-nitrobenzoate



2.96 g (13.7 mmol) of methyl 4-chloro-3-nitrobenzoate and 1.90 g (13.7 mmol) of potassium carbonate are successively added to a solution of 3.22 g (12.5 mmol) of the compound from Example 14A in 30 ml of DMF. The mixture is stirred at an oil bath temperature of 70°C for 5 h. Cooling to RT is followed by dilution with 200 ml of ethyl acetate. After washing with water and drying over magnesium sulphate, the volatile constituents are removed in vacuo. The residue is chromatographed on silica gel (ethyl acetate:cyclohexane 1:5). 4.3 g (79% of theory) of the desired product are obtained.

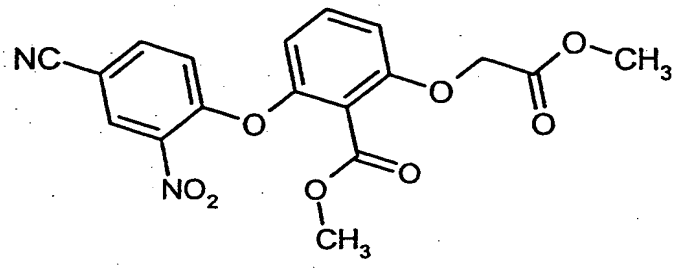
LC-MS (method 3): R_t = 3.67 min,

MS (ESI): m/z = 438 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.68 (s, 3H), 3.90 (s, 3H), 5.23 (s, 2H), 6.89 (d, 1H), 7.12 (d, 1H), 7.20 (d, 1H), 7.40 (m, 5H), 7.54 (dd, 1H), 8.19 (d, 1H), 8.51 (d, 1H).

Example 18A

Methyl 2-(4-cyano-2-nitrophenoxy)-6-(2-methoxy-2-oxoethoxy)benzoate



Preparation takes place in analogy to Example 17A from 1.52 g (6.33 mmol) of the compound from Example 15A, 1.27 g (6.96 mmol) of 4-chloro-2-nitrobenzonitrile and 960 mg (6.96 mmol) of potassium carbonate in 15 ml of DMF. The crude product is chromatographed on silica gel (ethyl acetate:cyclohexane 1:5). 2.21 g (90% of theory) of the desired product are obtained.

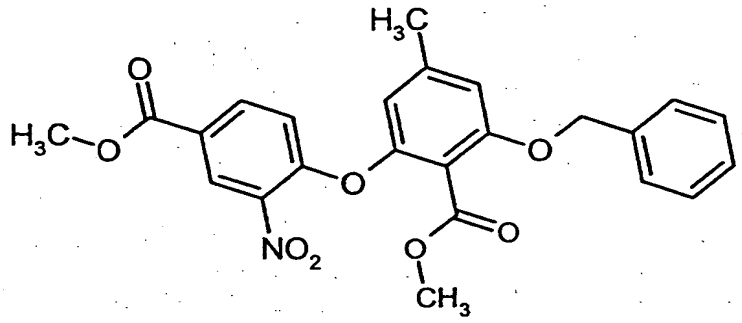
LC-MS (method 2): R_t = 3.40 min,

MS (ESI): m/z = 409 $(M+Na)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.68 (s, 3H), 3.72 (s, 3H), 4.95 (s, 2H), 6.93 (d, 1H), 7.04 (d, 1H), 7.11 (d, 1H), 7.52 (dd, 1H), 8.10 (d, 1H), 8.68 (s, 1H).

Example 19A

Methyl 2-(benzyloxy)-6-[4-(methoxycarbonyl)-2-nitrophenoxy]-4-methylbenzoate



Preparation takes place in analogy to Example 17A from 2.20 g (8.1 mmol) of the compound from Example 16A and 1.92 g (8.9 mmol) of methyl 4-chloro-3-nitrobenzoate. The crude product is chromatographed on silica gel (ethyl acetate: cyclohexane 1:5). 1.0 g (27% of theory) of the desired product is obtained.

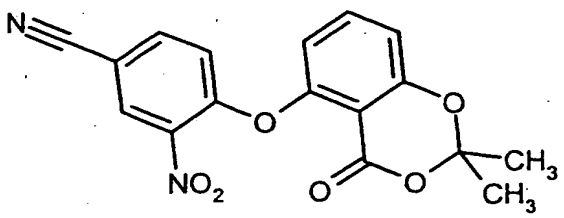
LC-MS (method 4): $R_t = 3.33$ min,

MS (ESI): $m/z = 452$ $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 2.33$ (s, 3H), 3.64 (s, 3H), 3.88 (s, 3H), 5.23 (s, 2H), 6.75 (s, 1H), 7.04 (s, 1H), 7.11 (d, 1H), 7.37 – 7.48 (m, 5H), 7.54 (dd, 1H), 8.19 (d, 1H), 8.51 (d, 1H).

Example 20A

4-[(2,2-Dimethyl-4-oxo-4*H*-1,3-benzodioxin-5-yl)oxy]-3-nitrobenzonitrile



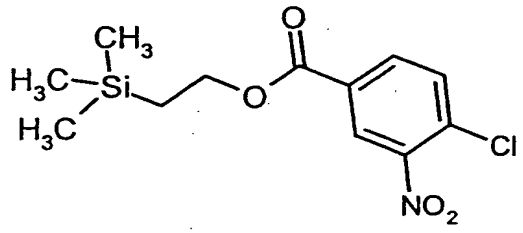
3.0 g (16.43 mmol) of 4-chloro-3-nitrobenzonitrile and 3.2 g (16.43 mmol) of 5-hydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are dissolved in 25 ml of DMF and, after addition of 2.498 g (18.08 mmol) of potassium carbonate, stirred at 70°C overnight. The mixture is worked up by pouring into 250 ml of water and extracting three times with ethyl acetate. The organic phase is dried over sodium sulphate and concentrated. 4.89 g (78% of theory) of product are obtained and are not purified further.

LC-MS (method 4): $R_t = 3.60$ min

MS (ESIpos): m/z = 341 $(M+H)^+$

Example 21A

2-(Trimethylsilyl)ethyl 4-chloro-3-nitrobenzoate

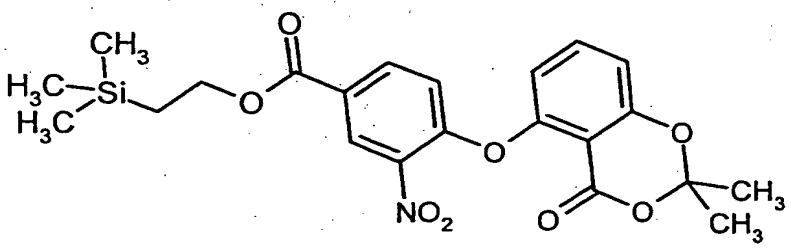


3.00 g (13.64 mmol) of 4-chloro-3-nitrobenzoyl chloride are dissolved in 8 ml of pyridine and, while cooling in ice, 1.93 g (16.36 mmol) of trimethylsilylethanol are added, and the mixture is then stirred at room temperature for 3 hours. The reaction mixture is worked up by diluting with toluene and washing with 1 N hydrochloric acid and saturated sodium chloride solution. The organic phase is dried over sodium sulphate and concentrated in vacuo. 3.99 g (87% of theory) of the product are obtained and are not purified further.

MS (EI): m/z = 319 $(M+NH_4)^+$

Example 22A

2-(Trimethylsilyl)ethyl 4-[(2,2-dimethyl-4-oxo-4*H*-1,3-benzodioxin-5-yl)oxy]-3-nitrobenzoate



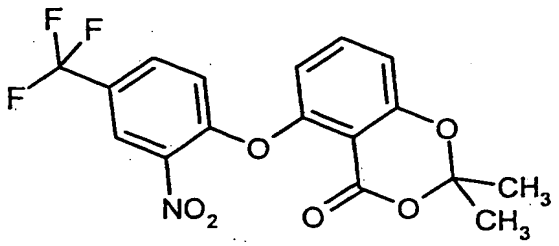
3.9 g (12.92 mmol) of 2-(trimethylsilyl)ethyl 4-chloro-3-nitrobenzoate and 2.51 g (12.92 mmol) of 5-hydroxy-2,2-dimethyl-4H-1,3-benzodioxin-4-one are dissolved in 25 ml of DMF and, after addition of 1.96 g (14.21 mmol) of potassium carbonate, stirred at 70°C overnight. The mixture is worked up by pouring into 250 ml of water and extracting three times with ethyl acetate. The organic phase is dried over sodium sulphate and concentrated. 5.91 g (84% of theory) of the product are obtained and are not purified further.

LC-MS (method 6): R_t = 1.30 min,

MS (ESIpos): m/z = 460 $(M+H)^+$

Example 23A

2,2-Dimethyl-5-[2-nitro-4-(trifluoromethyl)phenoxy]-4*H*-1,3-benzodioxin-4-one

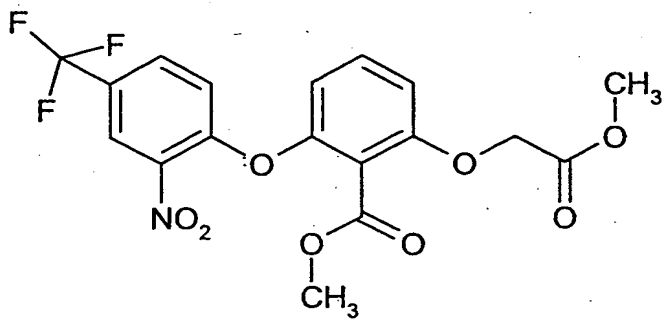


3.7 g (13.7 mmol) of 1-bromo-2-nitro-4-(trifluoromethyl)benzene and 2.66 g (13.70 mmol) of 5-hydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are dissolved in 25 ml of DMF and, after addition of 2.08 g (15.07 mmol) of potassium carbonate, stirred at 70°C overnight. The mixture is worked up by pouring into 250 ml of water and extracting three times with ethyl acetate. The organic phase is dried over sodium sulphate and concentrated. 5.16 g (95% of theory) of product are obtained.

LC-MS (method 7): R_t = 3.95 min,
MS (ESIpos): m/z = 384 $(M+H)^+$

Example 24A

Methyl 2-(2-methoxy-2-oxoethoxy)-6-[2-nitro-4-(trifluoromethyl)phenoxy]benzoate



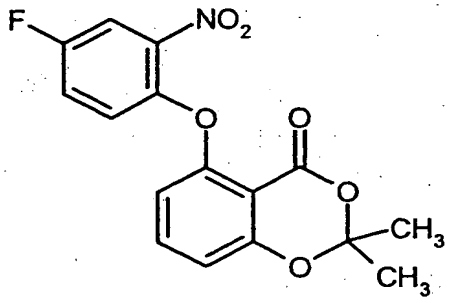
2 000 mg (8.33 mmol) of methyl 2-hydroxy-6-(2-methoxy-2-oxoethoxy)benzoate and 2 066 mg (9.16 mmol) of 1-chloro-2-nitro-4-(trifluoromethyl)benzene are dissolved in 30 ml of *N*,*N*-dimethylformamide and, after addition of 1 266 mg (9.16 mmol) of potassium carbonate, stirred at 70°C for 4 hours. After cooling, the mixture is diluted with water and extracted three times with ethyl acetate. The organic phase is washed with sodium chloride solution and dried over sodium sulphate. The volatile constituents are removed in vacuo. The crude product is purified on silica gel (mobile phase: methylene chloride/ethyl acetate 20:1). 2 965 mg (82% of theory) of product are obtained.

LC-MS (method 4): R_t=2.94 min,

MS (ESIpos): m/z = 430 $(M+H)^+$

Example 25A

5-(4-Fluoro-2-nitrophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one



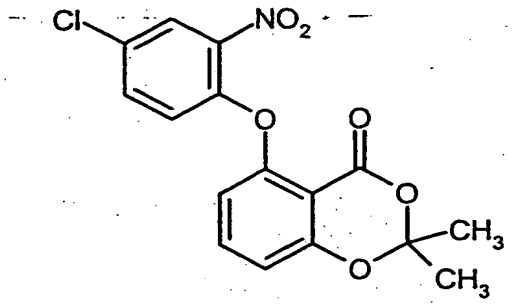
2.0 g (10.3 mmol) of 5-hydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are dissolved in 20 ml of anhydrous DMF under argon, and 1.64 g (10.3 mmol) of 2,5-difluoronitrobenzene and 1.42 g (10.3 mmol) of anhydrous potassium carbonate are added. The mixture is then stirred at 70°C overnight. For working up, the DMF is removed in vacuo, and the residue is taken up in ethyl acetate, washed twice with water and once with saturated sodium chloride solution and finally dried over magnesium sulphate. Purification takes place by column chromatography (silica gel: cyclohexane/dichloromethane 3:1). This results in 2 g (52% of theory) of product.

HPLC (method 8): R_t = 4.74 min

MS (DCI): m/z = 334 $(M+H)^+$

Example 26A

5-(4-Chloro-2-nitrophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one



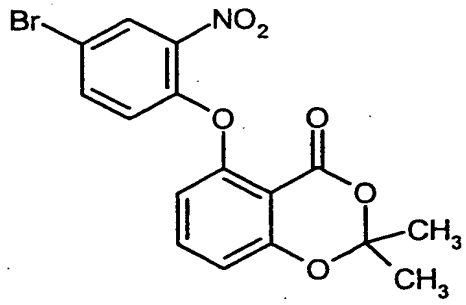
2.0 g (10.3 mmol) of 5-hydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are dissolved in 34 ml of anhydrous DMF under argon, and 1.81 g (10.3 mmol) of 5-chloro-2-fluoronitrobenzene and 1.42 g (10.3 mmol) of anhydrous potassium carbonate are added. The mixture is then stirred at 70°C overnight. For working up, it is diluted with ethyl acetate and washed several times with water and saturated sodium chloride solution. Drying over magnesium sulphate is followed by purification by column chromatography (silica gel: cyclohexane/ethyl acetate 10:1 to 2:1). 2.79 g (76% of theory) of product are obtained.

HPLC (method 8): R_t = 4.81 min

MS (DCI): m/z = 350 $(M+H)^+$

Example 27A

5-(4-Bromo-2-nitrophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one



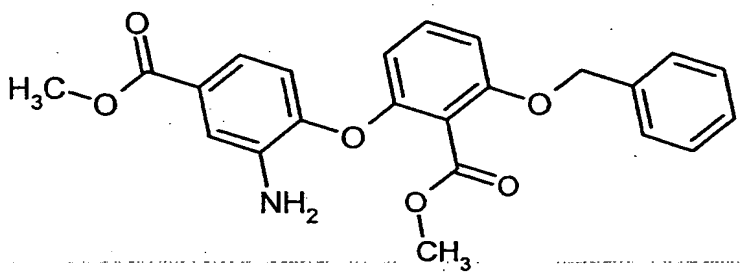
2.0 g (10.3 mmol) of 5-hydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are dissolved in 20 ml of anhydrous DMF under argon, and 2.27 g (10.3 mmol) of 5-bromo-2-fluoronitrobenzene and 1.42 g (10.3 mmol) of anhydrous potassium carbonate are added. The mixture is then stirred at 70°C overnight. For working up, the DMF is removed in vacuo, and the residue is taken up in ethyl acetate and washed three times with water. Drying over magnesium sulphate is followed by purification by column chromatography (silica gel: cyclohexane/ethyl acetate 4:1). 3.0 g (75% of theory) of product are obtained.

HPLC (method 8): $R_t = 4.86$ min

MS (DCI): $m/z = 411$ $(M+NH_4)^+$

Example 28A

Methyl 3-amino-4-[3-(benzyloxy)-2-(methoxycarbonyl)phenoxy]benzoate



A solution of 4.30 g (9.8 mmol) of the compound from Example 17A in 120 ml of methanol is mixed with 11.1 g (49.2 mmol) of tin(II) chloride dihydrate. The mixture is stirred at 70°C for 4 h and then concentrated in vacuo. The residue is stirred with 200 ml each of water and ethyl acetate, and the aqueous phase is adjusted to pH 8 by adding sodium bicarbonate. The resulting suspension is filtered through Celite. It is then possible to separate the phases, and the aqueous phase is extracted with ethyl acetate. The combined extracts are washed with water, dried over magnesium sulphate and concentrated in vacuo. The residue is chromatographed on silica gel

(ethyl acetate:cyclohexane 1:3). 2.2 g (55% of theory) of the desired product are obatined.

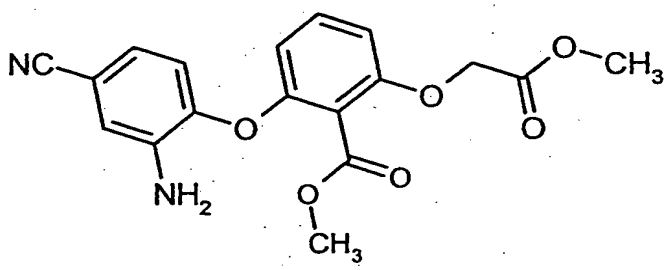
LC-MS (method 4): R_t = 3.02 min,

MS (ESI): m/z = 408 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.76 (s, 3H), 3.81 (s, 3H), 5.20 (s, 2H), 5.25 (s, 2H), 6.48 (d, 1H), 6.81 (d, 1H), 6.98 (d, 1H), 7.15 (d, 1H), 7.38 (m, 7H).

Example 29A

Methyl 2-(2-amino-4-cyanophenoxy)-6-(2-methoxy-2-oxoethoxy)benzoate



Preparation takes place in analogy to Example 28A from 1.20 g (3.11 mmol) of the compound from Example 18A in 50 ml of methanol and 3.50 g (15.5 mmol) of tin(II) chloride dihydrate. 1.02 g (92% of theory) of the desired product are obtained.

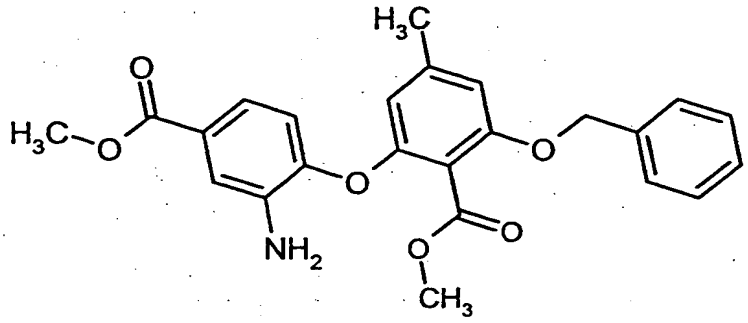
LC-MS (method 2): R_t = 3.30 min,

MS (ESI): m/z = 457 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.70 (s, 3H), 3.77 (s, 3H), 4.89 (s, 2H), 5.43 (s, br, 2H), 6.55 (d, 1H), 6.80 (d, 1H), 6.83 (dd, 1H), 6.94 (dd, 1H), 7.10 (s, 1H), 7.37 (dd, 1H).

Example 30A

Methyl 2-[2-amino-4-(methoxycarbonyl)phenoxy]-6-(benzyloxy)-4-methylbenzoate



Preparation takes place in analogy to Example 28A from 1.00 g (2.22 mmol) of the compound from Example 19A. The crude product is chromatographed on silica gel (ethyl acetate:cyclohexane 1:3). 700 mg (75% of theory) of the desired product are obtained.

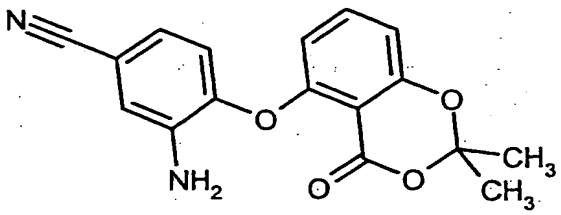
LC-MS (method 7): R_t = 3.61 min,

MS (ESI): m/z = 422 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 2.24 (s, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 5.19 (s, 2H), 5.25 (s, 2H), 6.30 (s, 1H), 6.80 (d, 1H), 6.84 (s, 1H), 7.15 (d, 1H), 7.38 (m, 6H).

Example 31A

3-Amino-4-[(2,2-dimethyl-4-oxo-4*H*-1,3-benzodioxin-5-yl)oxy]benzonitrile



4.87 g (14.31 mmol) of 4-[(2,2-dimethyl-4-oxo-4H-1,3-benzodioxin-5-yl)oxy]-3-nitrobenzonitrile are dissolved in a mixture of 60 ml of acetic acid and 3 ml of

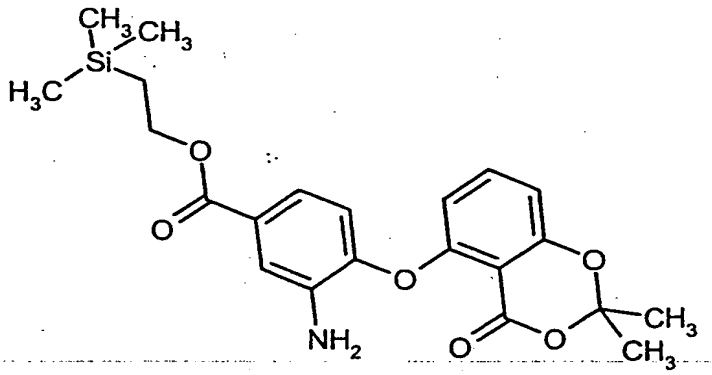
water, and 5.595 g (100.18 mmol) of iron powder are added. The suspension is stirred at RT for 1 hour and at 50°C for 3 hours. Cooling is followed by dilution with 300 ml of acetone, filtration with suction through Celite and washing with a large amount of acetone. The filtrate is concentrated and suspended in methylene chloride/ethyl acetate 5:1. The precipitate is filtered off with suction, and drying results in 1.46 g (32% of theory) of the product, which is not purified further.

LC-MS (method 2): $R_t = 3.50$ min

MS (ESIpos): $m/z = 311$ $(M+H)^+$

Example 32A

2-(Trimethylsilyl)ethyl 3-amino-4-[(2,2-dimethyl-4-oxo-4*H*-1,3-benzodioxin-5-yl)oxy]benzoate



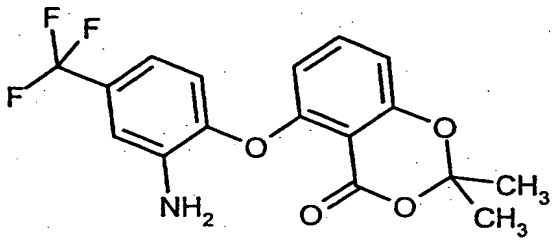
5.9 g (12.84 mmol) of 2-(trimethylsilyl)ethyl-4-[(2,2-dimethyl-4-oxo-4*H*-1,3-benzodioxin-5-yl)oxy]-3-nitrobenzoate are dissolved in a mixture of 60 ml (1 048.09 mmol) of acetic acid and 3 ml of water, and 5.019 g (89.88 mmol) of iron powder are added. The suspension is stirred at RT for 1 hour and at 50°C for 3 hours. Cooling is followed by dilution with 300 ml of acetone, filtration with suction through Celite and washing with a large amount of acetone. The filtrate is concentrated and suspended in methylene chloride/ethyl acetate 5:1 and again concentrated, and the residue is purified on silica gel (mobile phase: methylene chloride/ethyl acetate 30:1). 3.52 g (63% of theory) of product are obtained.

LC-MS (method 6): R_t = 1.06 min

MS (ESIpos): m/z = 430 $(M+H)^+$

Example 33A

5-[2-Amino-4-(trifluoromethyl)phenoxy]-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one



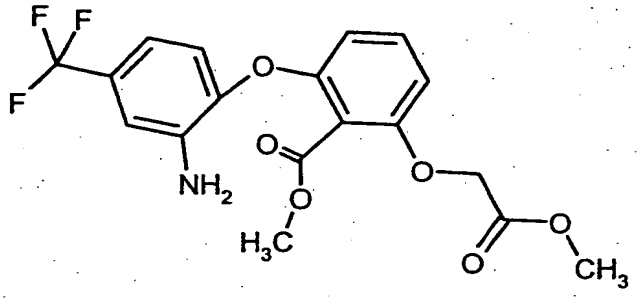
5.15 g (13.44 mmol) of 2,2-dimethyl-5-[2-nitro-4-(trifluoromethyl)phenoxy]-4*H*-1,3-benzodioxin-4-one are dissolved in 100 ml of a 1:1 ethyl acetate/ethanol mixture at RT. 1.43 g (1.34 mmol) of 10% palladium on carbon and 5.084 g (80.62 mmol) of ammonium formate are added, and the mixture is stirred at 80°C overnight. After the mixture has cooled, the catalyst is filtered off through Celite and washed with ethanol. The crude product is purified on silica gel (mobile phase: methylene chloride/ethyl acetate 30:1). 3.54 g (65% of theory) of product are obtained.

LC-MS (method 2): R_t = 3.70 min

MS (ESIpos): m/z = 354 $(M+H)^+$

Example 34A

Methyl {[11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetate



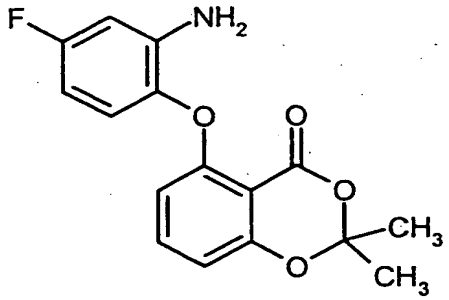
2 940.0 mg (6.85 mmol) of methyl 2-(2-methoxy-2-oxoethoxy)-6-[2-nitro-4-(trifluoromethyl)phenoxy]benzoate are dissolved in a mixture of ethyl acetate and ethanol in the ratio of 1:1 (total 10 ml). Addition of 729 mg (0.68 mmol) of Pd/C (10%) and 2 591 mg (41.1 mmol) of ammonium formate is followed by stirring at 80°C for 2 hours. After the reaction mixture has cooled it is filtered through a silica gel frit. It is washed with ethanol, and the volatile constituents are removed in vacuo. 2 477 mg (86% of theory) of the product are obtained and are not purified further.

LC-MS (method 5): R_t=3.42 min

MS (ESIpos): m/z = 400 $(M+H)^+$

Example 35A

5-(2-Amino-4-fluorophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one



1.9 g (5.70 mmol) of 5-(4-fluoro-2-nitrophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are dissolved in 15 ml of ethanol, and 300 mg of palladium hydroxide on

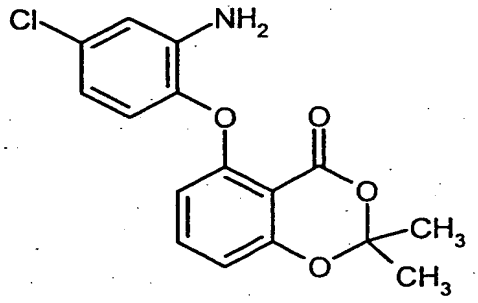
carbon (20%) are added. The mixture is then stirred under a hydrogen atmosphere until reaction is complete. It is worked up by filtration through Celite, washing with ethanol. Since the filtrate still contains traces of carbon, it is again filtered through Celite (provided with a thin silica gel layer) and washed with ethanol. Concentration and drying in vacuo result in 1.5 g (87% of theory) of product.

HPLC (method 8): $R_t = 4.48$ min

MS (DCI): $m/z = 304$ $(M+H)^+$

Example 36A

5-(2-Amino-4-chlorophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one



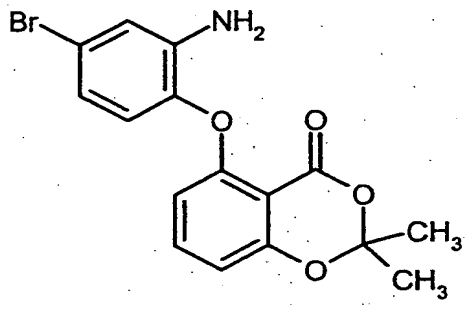
1 g (2.86 mmol) of 5-(4-chloro-2-nitrophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are mixed with 10 ml of acetic acid and 0.5 ml of water. Then 1.12 g (20 mmol) of iron are added, and the mixture is heated to 50°C. It is stirred at this temperature until reaction is complete. Cooling to RT is followed by dilution with acetone and filtration through Celite. The filtrate is concentrated in vacuo. Addition of toluene and evaporation to dryness is then carried out twice. The residue is taken up in ethyl acetate and filtered through silica gel. The filtrate is concentrated and dried in vacuo. 0.92 g (99% of theory) of crude product is obtained and is not purified further.

HPLC (method 8): $R_t = 4.62$ min

MS (DCI): $m/z = 320$ $(M+H)^+$

Example 37A

5-(2-Amino-4-bromophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one



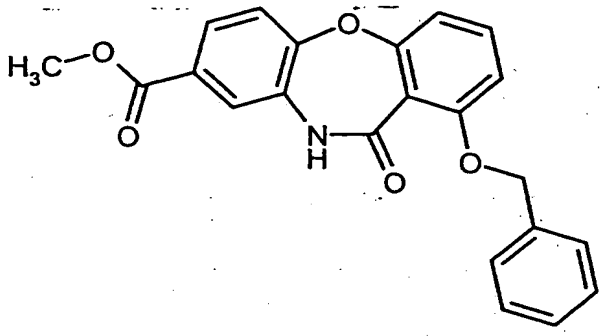
1 g (2.54 mmol) of 5-(4-bromo-2-nitrophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one is mixed with 10 ml of acetic acid and 0.5 ml of water. Then 992 mg (17.8 mmol) of iron are added, and the mixture is heated to 50°C. It is stirred at this temperature until reaction is complete. Cooling to RT is followed by dilution with acetone and filtration through Celite. The filtrate is concentrated in vacuo. Addition of toluene and evaporation to dryness is then carried out twice. The residue is taken up in ethyl acetate and filtered through silica gel. The filtrate is concentrated and dried in vacuo. 0.89 g (95% of theory) of crude product is obtained and is not purified further.

HPLC (method 8): $R_t = 4.60$ min

MS (DCI): m/z = 364 $(M+H)^+$

Example 38A

Methyl 1-benzyloxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



A solution of 2.20 g (5.1 mmol) of the compound from Example 28A in 200 ml of toluene is mixed with 193 mg (1.0 mmol) of p-toluenesulphonic acid hydrate and stirred at the reflux temperature overnight. Cooling to RT is followed by concentration in vacuo. The residue is chromatographed on silica gel (cyclohexane:ethyl acetate 3:1). 1.49 g (78% of theory) of the desired compound are obtained.

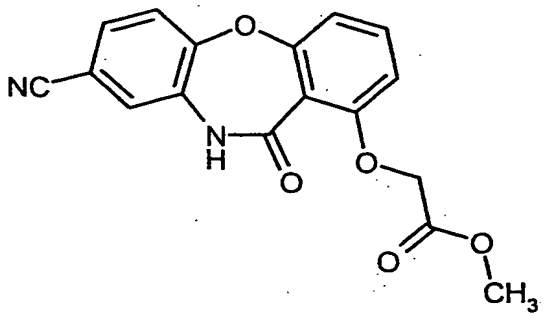
LC-MS (method 3): R_t = 3.35 min,

MS (ESI): m/z = 376 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.81 (s, 3H), 5.17 (s, 2H), 6.95 (d, 1H), 7.05 (d, 1H), 7.28 - 7.55 (m, 7H), 7,69 (m, 2H).

Example 39A

Methyl [(8-cyano-11-oxo-10,11-dihydrodibenzo[*b,f*][1,4]oxazepin-1-yl)oxy]acetate

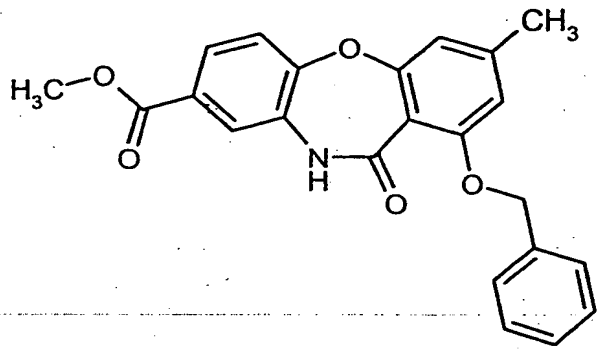


A solution of 791 mg (2.22 mmol) of the compound from Example 29A in 250 ml of toluene is mixed with 76 mg (0.44 mmol) of para-toluenesulphonic acid hydrate. The mixture is heated at the reflux temperature overnight. Cooling to RT is followed by washing once with saturated aqueous sodium bicarbonate solution, drying over magnesium sulphate and concentration in vacuo. The resulting product is reacted without further purification.

LC-MS (method 2): R_t = 3.02 min,
MS (ESI): m/z = 325 $(M+H)^+$.

Example 40A

Methyl 1-(benzyloxy)-3-methyl-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepin-8-carboxylate

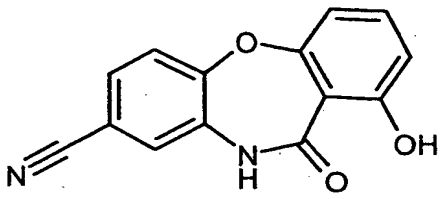


Preparation takes place in analogy to Example 38A from 700 mg (1.66 mmol) of the compound from Example 30A. The crude product is chromatographed on silica gel (cyclohexane:ethyl acetate 3:1). 448 mg (67% of theory) of the desired compound are obtained.

LC-MS (method 3): R_t = 3.41 min,
MS (ESI): m/z = 390 $(M+H)^+$.
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.32 (s, 3H), 3.83 (s, 3H), 5.16 (s, 2H), 6.82 (s, 1H), 6.92 (s, 1H), 7.31 (dd, 1H), 7.40 (m, 3H), 7.49 (m, 2H), 7.71 (m, 2H), 10.47 (s, 1H).

Example 41A

1-Hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carbonitrile



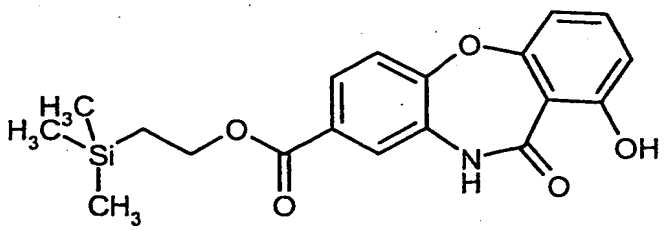
2.9 g (7.29 mmol) of 78% pure 3-amino-4-[(2,2-dimethyl-4-oxo-4*H*-1,3-benzodioxin-5-yl)oxy]benzonitrile are dissolved in 50.0 ml of xylene at RT, and 0.139 g (0.73 mmol) of 4-toluenesulphonic acid monohydrate is added. The suspension is stirred at 140°C overnight. After the reaction mixture has been cooled, the precipitate is filtered off with suction and washed with cyclohexane. The precipitate is then suspended in methanol and filtered with suction several times, and subsequently dried under high vacuum. 2.33 g (95% of theory) of the product are obtained and are not purified further.

LC-MS (method 2): $R_t = 3.40$ min

MS (ESIpos): m/z = 253 $(M+H)^+$

Example 42A

2-(Trimethylsilyl)ethyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



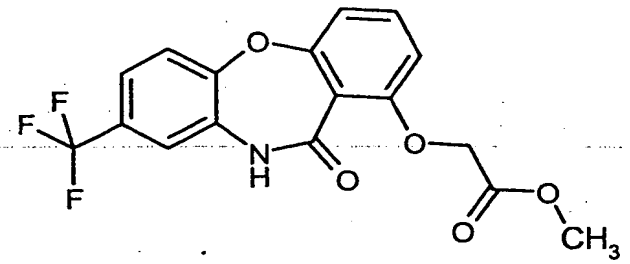
3.5 g (8.15 mmol) of 2-(trimethylsilyl)ethyl 3-amino-4-[(2,2-dimethyl-4-oxo-4*H*-1,3-benzodioxin-5-yl)oxy]benzoate are dissolved in 50.0 ml of xylene at RT, and 0.155 g (0.82 mmol) of 4-toluenesulphonic acid monohydrate is added. The suspension is stirred at 140°C overnight. After the reaction mixture has been cooled, the precipitate is filtered off with suction and washed with cyclohexane. The precipitate is then suspended in methanol and filtered off with suction several times. After drying, the residue is taken up in 1N sodium hydroxide solution and extracted with ethyl acetate. The organic phase is dried over sodium sulphate and concentrated. 0.734 g (24% of theory) of the product are obtained and are not purified further.

LC-MS (method 2): $R_t = 3.20$ min

MS (ESIpos): $m/z = 372$ $(M+H)^+$

Example 43A

Methyl {[11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetate



2.45 g (5.83 mmol) of methyl 2-[2-amino-4-(trifluoromethyl)phenoxy]-6-(2-methoxy-2-oxoethoxy)benzoate are dissolved in 1 400.0 ml of xylene at RT, and 0.221 g (1.17 mmol) of 4-toluenesulphonic acid monohydrate is added. The suspension is stirred at 140°C overnight. After the reaction mixture has been cooled, the precipitate is filtered off with suction and washed with cyclohexane. The precipitate is then suspended in methanol and filtered off with suction several times

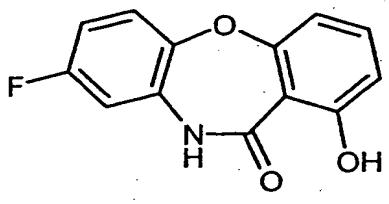
and subsequently dried under high vacuum. 0.583 g (27% of theory) of the product are obtained and are not purified further.

LC-MS (method 4): $R_t = 2.65$ min

MS (ESIpos): m/z = 368 $(M+H)^+$

Example 44A

8-Fluoro-1-hydroxydibenzo[b,f][1,4]oxazepin-11(10*H*)-one



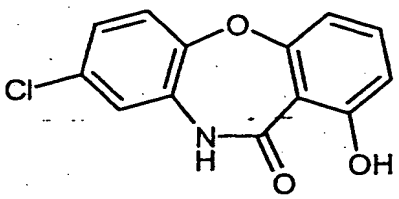
1.5 g (4.95 mmol) of 5-(2-amino-4-fluorophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are mixed with 20 ml of xylene and 94 mg (0.49 mmol) of p-toluenesulphonic acid monohydrate. The reaction mixture is stirred at 120°C overnight and then concentrated in vacuo. The resulting residue is stirred in methanol, and the resulting solid is filtered off and dried in vacuo. 948 mg (78% of theory) of product are obtained.

HPLC (method 9): $R_t = 4.47$ min

MS (DCI): m/z = 246 $(M+H)^+$

Example 45A

8-Chloro-1-hydroxydibenzo[b,f][1,4]oxazepin-11(10*H*)-one



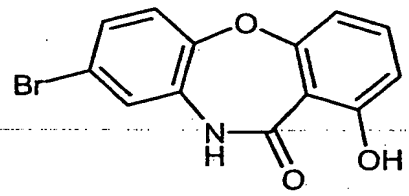
919 mg (2.87 mmol) of 5-(2-amino-4-chlorophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are mixed with 12 ml of xylene and 55 mg (0.29 mmol) of p-toluenesulphonic acid monohydrate. The reaction mixture is stirred under reflux overnight and then concentrated in vacuo. The resulting residue is stirred in methanol, and the resulting solid is filtered off and dried in vacuo. 671 mg (88% of theory) of product are obtained.

HPLC (method 8): $R_t = 4.74$ min

MS (DCI): m/z = 262 $(M+H)^+$

Example 46A

8-Bromo-1-hydroxydibenzo[b,f][1,4]oxazepin-11(10*H*)-one



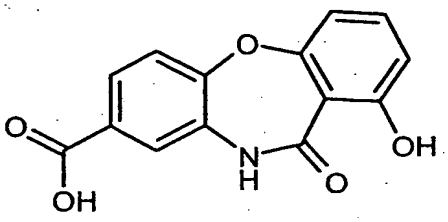
892 mg (2.45 mmol) of 5-(2-amino-4-bromophenoxy)-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one are mixed with 10 ml of xylene and 47 mg (0.24 mmol) of p-toluenesulphonic acid monohydrate. The reaction mixture is stirred under reflux overnight. Since the reaction is not yet complete, a further 47 mg (0.24 mmol) of p-toluenesulphonic acid monohydrate are added, and the mixture is stirred under reflux for a further 24 hours. It is concentrated in vacuo, and the resulting residue is stirred in methanol. The resulting solid is filtered off and dried in vacuo. 581 mg (78% of theory) of product are obtained.

HPLC (method 8): $R_t = 4.71$ min

MS (DCI): m/z = 306 $(M+H)^+$

Example 47A

1-Hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylic acid



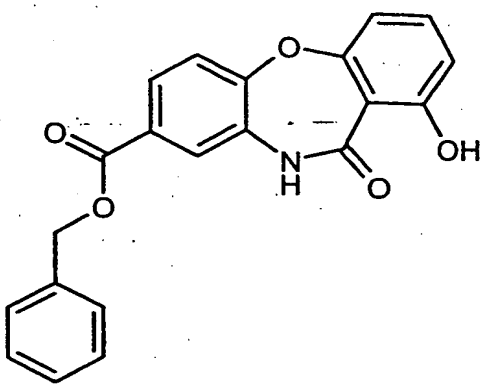
4.32 g (15.14 mmol) of methyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-8-carboxylate are dissolved in 33 ml of THF and, after addition of 0.798 g (33.32 mmol) of lithium hydroxide in 33 ml of water, stirred at RT overnight. The mixture is worked up by acidification with 1N hydrochloric acid and removal of most of the solvent in vacuo. The precipitate is filtered off with suction and dried under high vacuum. 4.443 g (quant.) of product are obtained and are not purified further.

LC-MS (method 7): $R_t = 2.96$ min

MS (ESIpos): m/z = 272 $(M+H)^+$

Example 48A

Benzyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



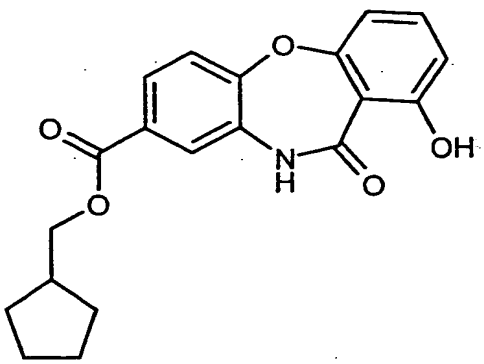
220 mg (0.81 mmol) of 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylic acid and 5.0 ml (49.18 mmol) of benzyl alcohol are mixed with 16 mg (0.16 mmol) of sulphuric acid and stirred at 150°C for 3 hours. The mixture is worked up by dilution with ethyl acetate and washing with saturated sodium carbonate solution and with sodium chloride solution. The organic phase is dried over sodium sulphate and concentrated. Purification is initially by preparative HPLC (method 11) and then on silica gel (mobile phase: methylene chloride/methanol 20:1). 122 mg (41% of theory) of the product are obtained.

LC-MS (method 3): $R_t = 3.92$ min

MS (ESIpos): m/z = 362 $(M+H)^+$

Example 49A

Cyclopentylmethyl-1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



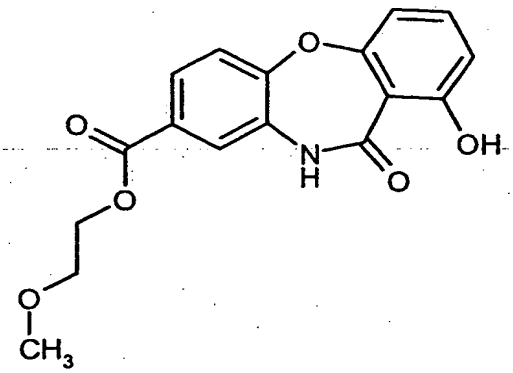
220 mg (0.81 mmol) of 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylic acid and 5.0 ml (49.18 mmol) of cyclopentylmethanol are mixed with 16 mg (0.16 mmol) of sulphuric acid and stirred at 160°C for 3 hours. The reaction mixture is worked up by concentrating somewhat, diluting with ethyl acetate and washing with saturated sodium carbonate solution and with sodium chloride solution. The organic phase is dried over sodium sulphate and concentrated. Drying in vacuo for 3 hours results in 270 mg (94% of theory) of the product, which is not purified further.

LC-MS (method 3): $R_t = 4.49$ min

MS (ESIpos): $m/z = 354$ $(M+H)^+$

Example 50A

2-Methoxyethyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



300 mg (1.11 mmol) of 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylic acid and 5.0 ml (63.41 mmol) of 2-methoxyethanol are mixed with 22 mg (0.22 mmol) of sulphuric acid and stirred under reflux for 3 hours. The reaction mixture is worked up by concentrating somewhat, diluting with ethyl acetate and washing with saturated sodium carbonate solution and with sodium chloride

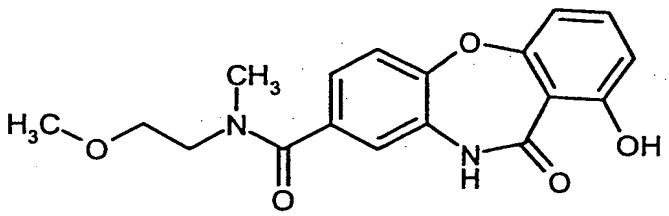
solution. The organic phase is dried over sodium sulphate and concentrated. 243 mg (61% of theory) of the product are obtained and are not purified further.

LC-MS (method 2): R_t = 3.60 min

MS (ESIpos): m/z = 330 $(M+H)^+$

Example 51A

1-Hydroxy-*N*-(2-methoxyethyl)-*N*-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-8-carboxamide



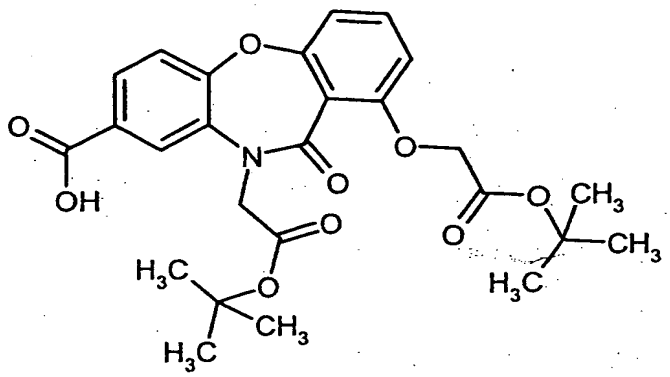
250 mg (0.92 mmol) of 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylic acid, 246 mg (2.77 mmol) of *N*-(2-methoxyethyl)-*N*-methylamine and 11 mg (0.09 mmol) of 4-dimethylaminopyridine are dissolved in 6 ml of DMF. The mixture is then cooled to -30°C. At this temperature, 212 mg (1.11 mmol) of *N*-ethyl-*N'*-3-(dimethylaminopropyl)carbodiimide hydrochloride are added, and the mixture is allowed to fall to RT again. It is stirred at RT for 4 hours. The mixture is worked up by dilution with water, addition of 1N hydrochloric acid and extraction with ethyl acetate. The organic phase is washed with saturated sodium carbonate solution and with sodium chloride solution, dried over sodium sulphate and concentrated. The crude product is purified on silica gel (mobile phase: ethyl acetate). 100 mg (30% of theory) of the product are obtained.

LC-MS (method 4): R_t = 4.00 min

MS (ESIpos): m/z = 343 $(M+H)^+$

Example 52A

1-(2-tert-Butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylic acid



110 mg (0.18 mmol) of 2-(trimethylsilyl)ethyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 5 ml of tetrahydrofuran and, at RT, 0.20 ml (0.20 mmol) of 1N tetra-*n*-butylammonium fluoride solution is added, and the mixture is stirred at RT overnight. It is mixed with a little water and, after addition of 1 ml of 1N hydrochloric acid, concentrated at RT. The residue is purified by preparative HPLC (method 11). 95 mg (100% of theory) of the product are obtained.

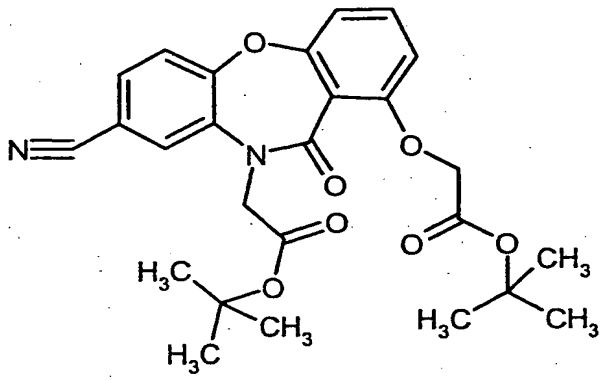
HPLC (method 7): R_t = 3.60 min

MS (ESIpos): m/z = 500 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.34 (s, 9H), 1.39 (s, 9H), 4.52-4.81 (m, 4 H), 6.82 (d, 1 H), 7.00 (d, 1 H), 7.39-7.50 (m, 2 H), 7.77 (dd, 1 H), 7.93 (s, 1H).

Example 53A

tert-Butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-cyano-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate



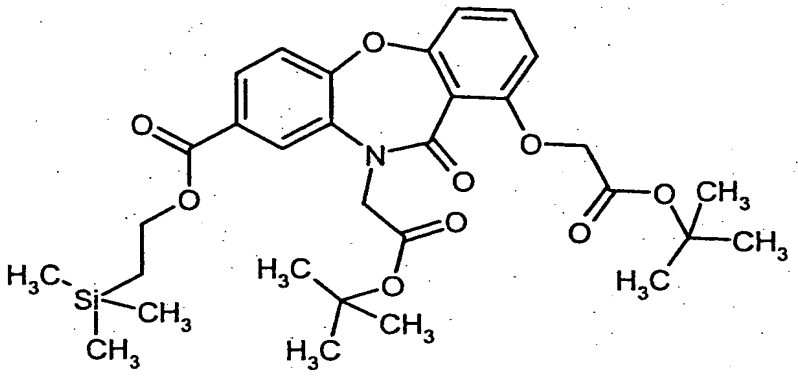
1.70 g (6.74 mmol) of 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carbonitrile are dissolved in 20 ml of DMF at RT, and 5.45 ml (26.96 mmol) of tert-butyl bromoacetate and 2.794 g (20.22 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min, at 50°C for 1 hour and at 70°C for 5 hours. The mixture is worked up by dilution with a large amount of water and extraction three times with ethyl acetate. The organic phase is washed with sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. 3.76 g (quant.) of the product are obtained.

LC-MS (method 7): R_t = 3.95 min

MS (ESIpos): m/z = 481 $(M+H)^+$

Example 54A

2-(Trimethylsilyl)ethyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



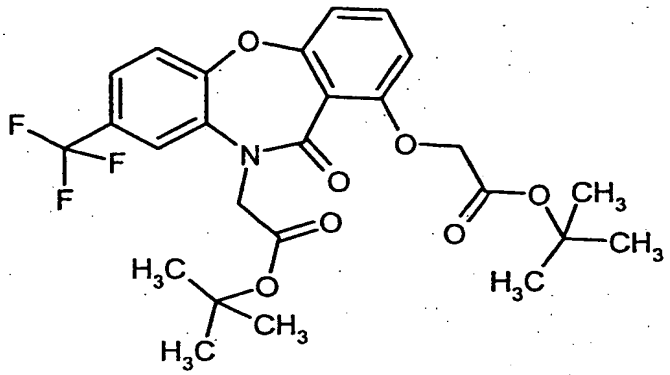
0.70 g (1.88 mmol) of 2-(trimethylsilyl)ethyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 8 ml of DMF at RT, and 0.84 ml (4.15 mmol) of tert-butyl bromoacetate and 0.521 g (3.77 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 50°C overnight. The mixture is worked up by dilution with a large amount of water and extraction three times with ethyl acetate. The organic phase is washed with sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. The residue is purified by preparative HPLC (method 11). 209 mg (15% of theory) of the product are obtained.

LC-MS (method 4): $R_t = 4.90$ min

MS (ESIpos): $m/z = 600$ $(M+H)^+$

Example 55A

tert-Butyl [1-(2-tert-butoxy-2-oxoethoxy)-11-oxo-8-(trifluoromethyl)dibenzo-[b,f][1,4]oxazepin-10(11*H*)-yl]acetate



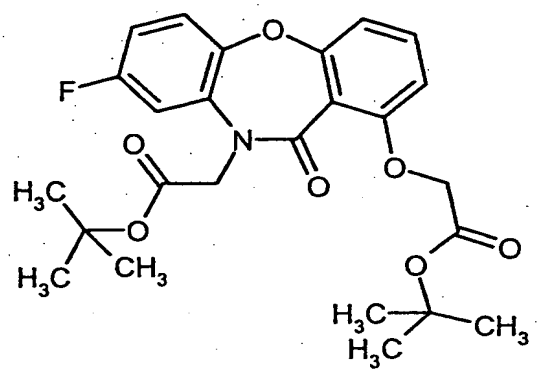
670 mg (2.27 mmol) of 1-hydroxy-8-(trifluoromethyl)dibenzo[b,f][1,4]oxazepin-11(10*H*)-one are dissolved in 20 ml of DMF at RT, and 1.835 ml (9.08 mmol) of tert-butyl bromoacetate and 627 mg (4.54 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 70°C overnight. The mixture is worked up by dilution with a large amount of water and extraction three times with ethyl acetate. The organic phase is washed with sodium chloride solution, dried over sodium sulphate and concentrated in vacuo. The residue is chromatographed on silica gel (mobile phase: dichloromethane/ethyl acetate 20:1). 1.185 g (99% of theory) of the product are obtained.

LC-MS (method 4): $R_t = 4.00$ min

MS (ESIpos): m/z = 524 $(M+H)^+$

Example 56A

tert-Butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-fluoro-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate



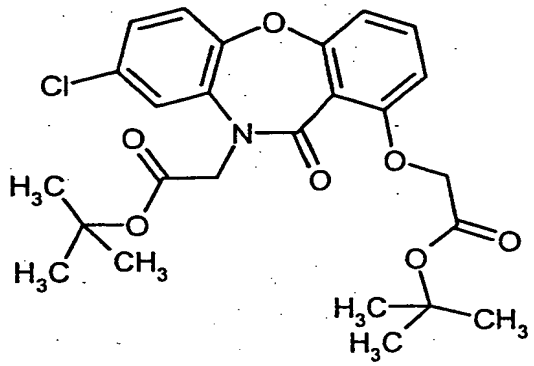
938 mg (3.83 mmol) of 8-fluoro-1-hydroxydibenzo[b,f][1,4]oxazepin-11(10*H*)-one are dissolved in 6 ml of anhydrous DMF, and 1.59 g (11.48 mmol) of anhydrous potassium carbonate are added. While stirring at RT, 1.87 g (9.56 mmol) of tert-butyl bromoacetate are added. The mixture is left to stir at RT overnight. It is worked up by diluting with ethyl acetate and washing twice with water and once with saturated sodium chloride solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. 2 g (quant.) of crude product are obtained and are not purified further.

HPLC (method 9): R_t = 5.17 min

MS (ESIpos): m/z = 474 $(M+H)^+$

Example 57A

tert-Butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-chloro-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate



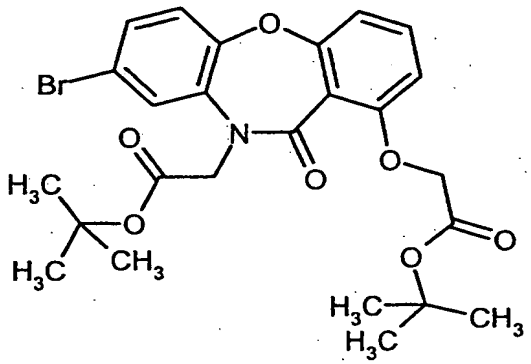
660 mg (2.52 mmol) of 8-chloro-1-hydroxydibenzo[b,f][1,4]oxazepin-11(10*H*)-one are dissolved in 6 ml of anhydrous DMF, and 1.05 g (7.57 mmol) of anhydrous potassium carbonate are added. While stirring at RT, 1.23 g (6.31 mmol) of tert-butyl bromoacetate are added. The mixture is left to stir at RT overnight. It is worked up by diluting with ethyl acetate and washing twice with water and once with saturated sodium chloride solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. 1.25 g (quant.) of crude product are obtained and are not purified further.

HPLC (method 9): R_t = 5.24 min

MS (DCI): m/z = 490 $(M+H)^+$

Example 58A

tert-Butyl [8-bromo-1-(2-tert-butoxy-2-oxoethoxy)-11-oxodibenzo[b,f][1,4]-oxazepin-10(11*H*)-yl]acetate



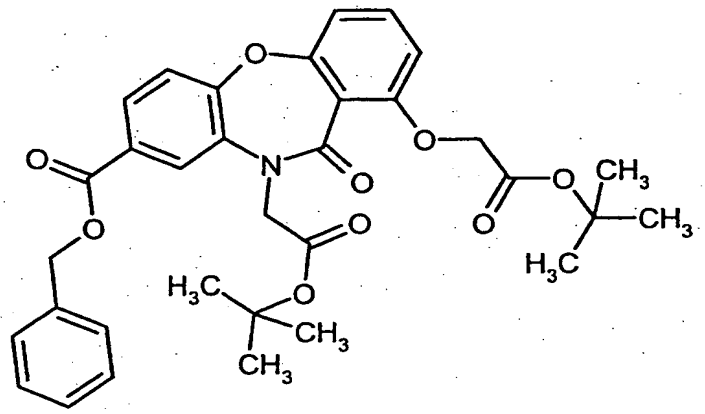
566 mg (1.85 mmol) of 8-bromo-1-hydroxydibenzo[b,f][1,4]oxazepin-11(10*H*)-one are dissolved in 10 ml of anhydrous DMF, and 766 mg (5.55 mmol) of anhydrous potassium carbonate are added. While stirring at RT, 901 mg (4.62 mmol) of tert-butyl bromoacetate are added. The mixture is left to stir at RT overnight. It is worked up by removing the solvent in vacuo, taking up the residue in ethyl acetate and washing three times with water. The organic phase is dried over magnesium sulphate, filtered and concentrated. 1.02 g (quant.) of crude product are obtained and are not purified further.

HPLC (method 8): $R_t = 5.34$

MS (ESIpos): $m/z = 534$ $(M+H)^+$

Example 59A

Benzyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



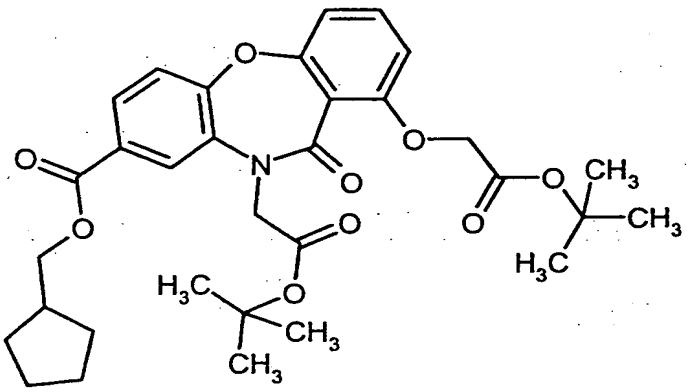
105 mg (0.291 mmol) of benzyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-8-carboxylate are dissolved in 3 ml of DMF at RT, and 0.129 ml (0.64 mmol) of tert-butyl bromoacetate and 80 mg (0.58 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 50°C overnight. The reaction mixture is worked up by dilution with a large amount of water and extraction three times with ethyl acetate. The organic phase is washed with sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. The residue is chromatographed on silica gel (mobile phase: dichloromethane/ethyl acetate 10:1). 123 mg (71% of theory) of the product are obtained.

LC-MS (method 7): R_t = 4.21 min

MS (ESIpos): m/z = 590 $(M+H)^+$

Example 60A

Cyclopentylmethyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



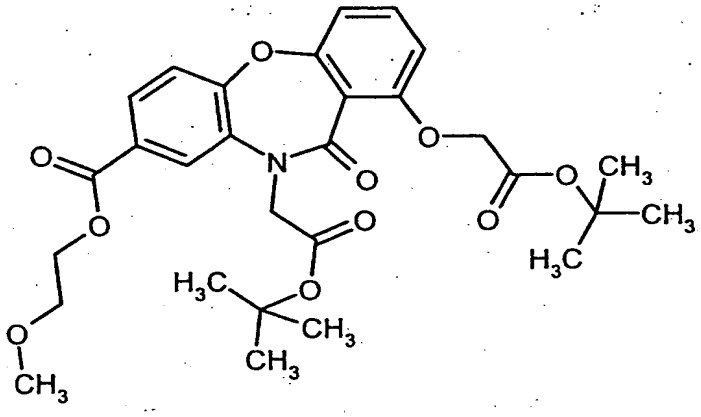
265 mg (0.75 mmol) of cyclopentylmethyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 3 ml of DMF at RT, and 0.333 ml (1.65 mmol) of tert-butyl bromoacetate and 207 mg (1.50 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 50°C overnight. The mixture is worked up by dilution with a large amount of water and extraction three times with ethyl acetate. The organic phase is washed with sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. The residue is chromatographed on silica gel (mobile phase: dichloromethane/ethyl acetate 10:1). 260.0 mg (59% of theory) of the product are obtained.

LC-MS (method 3): $R_t = 4.93$ min

MS (ESIpos): m/z = 582 $(M+H)^+$

Example 61A

2-Methoxyethyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



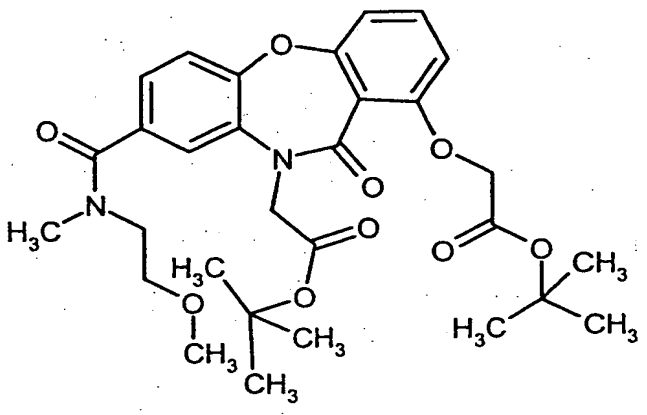
225 mg (0.68 mmol) of 2-methoxyethyl-1-hydroxyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 3 ml of DMF at RT, and 0.28 ml (1.37 mmol) of tert-butyl bromoacetate and 189 mg (1.37 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 50°C overnight. The mixture is worked up by dilution with a large amount of water and extraction three times with ethyl acetate. The organic phase is washed with sodium chloride solution, dried over magnesium sulphate and concentrated in vacuo. The residue is chromatographed on silica gel (mobile phase: dichloromethane/ethyl acetate 10:1). 248 mg (61% of theory) of the product are obtained.

LC-MS (method 2): R_t = 4.00 min

MS (ESIpos): m/z = 558 $(M+H)^+$

Example 62A

tert-Butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-{[(2-methoxyethyl)(methyl)amino]-carbonyl}-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate



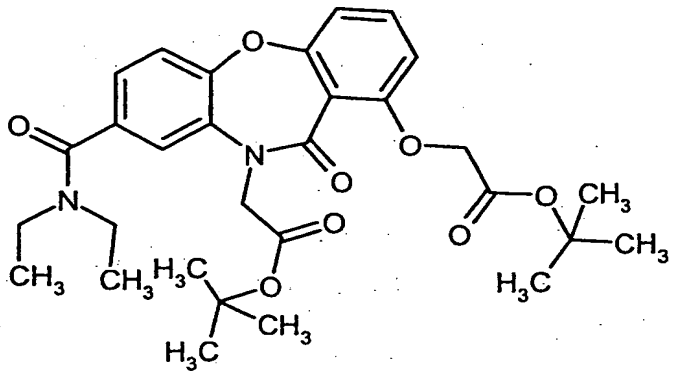
85 mg (0.25 mmol) of 1-hydroxy-*N*-(2-methoxyethyl)-*N*-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxamide are dissolved in 6 ml of DMF at RT, and 0.11 ml (0.55 mmol) of tert-butyl bromoacetate and 69 mg (0.50 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 50°C overnight. The mixture is worked up by dilution with a large amount of water, extraction three times with ethyl acetate and washing with sodium chloride solution. The organic phase is dried over sodium sulphate, the solvent is evaporated off, and the residue is dried. 136.0 mg (94% of theory) of the product are obtained.

LC-MS (method 4): R_t = 4.30 min

MS (ESIpos): m/z = 571 $(M+H)^+$

Example 63A

tert-Butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-[(diethylamino)carbonyl]-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate



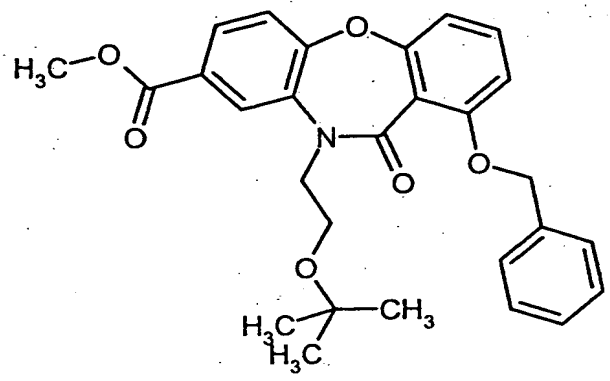
75 mg (0.150 mmol) of 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylic acid are dissolved with 28 mg (0.23 mmol) of DMAP and 114 mg (0.30 mmol) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in 4 ml of DMF at RT and then 0.031 ml (0.30 mmol) of diethylamine is added. The mixture is stirred at RT overnight. The reaction solution is worked up by dilution with water and extraction with ethyl acetate. The organic phase is washed once each with sodium carbonate solution and sodium chloride solution. The organic phase is dried over magnesium sulphate and concentrated in vacuo. The residue is filtered with suction through a silica gel frit (mobile phase: ethyl acetate) and concentrated in vacuo. 74 mg (85% of theory) of product are obtained.

LC-MS (method 3): R_t = 4.24 min

MS (ESIpos): m/z = 555 $(M+H)^+$

Example 64A

Methyl 1-benzyloxy-10-(2-tert-butoxyethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-8-carboxylate



255 mg (1.2 mmol) of 2-tert-butoxyethyl bromide, 276 mg (2.0 mmol) of potassium carbonate and 26.5 mg (0.16 mmol) of potassium iodide are successively added to a solution of 300 mg (0.8 mmol) of the compound from Example 38A in 0.06 ml of DMF/12 ml of 1,4-dioxane. The mixture is stirred at an oil bath temperature of 60°C for 1 h and then at the reflux temperature for 30 h. Cooling to RT is followed by dilution with 100 ml of dichloromethane and washing with water. The organic phase is dried over magnesium sulphate and concentrated in vacuo. 411 mg (95% of theory) of the desired product are obtained.

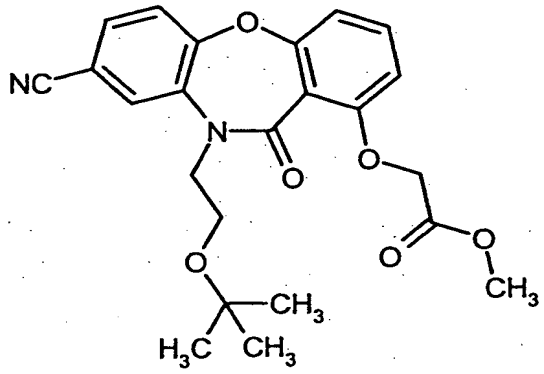
LC-MS (method 4): R_t = 3.37 min,

MS (ESI): m/z = 476 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.07 (s, 9H), 3.58 (m, 2H), 3.79 (m, 1H), 3.81 (s, 3H), 4.35 (m, 1H), 5.10 (d, 1H), 5.19 (d, 1H), 6.96 (d, 1H), 7.04 (d, 1H), 7.28 - 7.49 (m, 7H), 7.77 (d, 1H), 8.59 (s, 1H).

Example 65A

Methyl {[10-(2-tert-butoxyethyl)-8-cyano-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]-oxazepin-1-yl]oxy}acetate



Preparation takes place in analogy to Example 64A from 125 mg (0.39 mmol) of the compound from Example 39A and 123 mg (0.58 mmol) of tert-butoxyethyl bromide. The crude product is chromatographed on silica gel (cyclohexane:ethyl acetate 3:1). 68 mg (41% of theory) of the desired product are obtained.

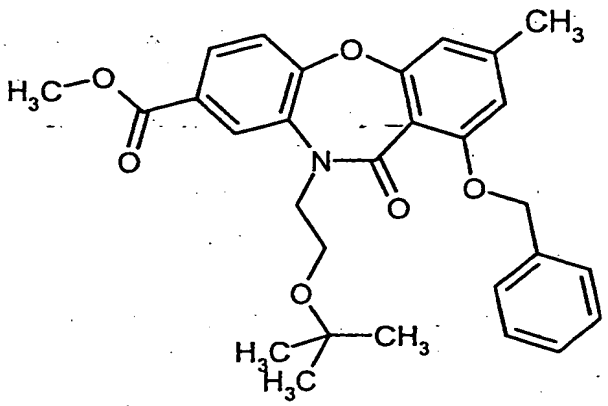
LC-MS (method 5): R_t = 3.38 min,

MS (ESI): m/z = 425 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.05 (s, 9H), 3.42 (m, 1H), 3.58 (m, 1H), 3.68 (s, 3H), 4.13 (m, 2H), 6.85 (d, 1H), 7.01 (d, 1H), 7.42 (dd, 1H), 7.53 (d, 1H), 7.70 (d, 1H), 8.36 (s, 1H).

Example 66A

Methyl 1-(benzyloxy)-10-(2-tert-butoxyethyl)-3-methyl-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine-8-carboxylate



Preparation takes place in analogy to Example 64A from 428 mg (1.10 mmol) of the compound from Example 40A and 398 mg (1.65 mmol) of tert-butoxyethyl bromide. 295 mg (55% of theory) of the desired product are obtained.

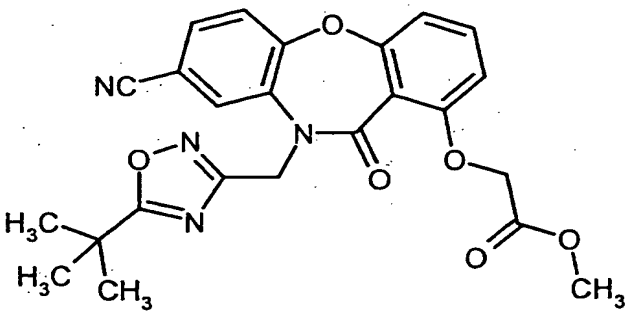
LC-MS (method 2): $R_t = 4.33$ min,

MS (ESI): $m/z = 490$ $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.05 (s, 9H), 2.31 (s, 3H), 3.58 (m, 2H), 3.62 (m, 2H), 3.81 (s, 3H), 3.82 (m, 1H), 4.33 (m, 1H), 5.08 (d, 1H), 5.14 (d, 1H), 6.81 (s, 1H), 6.90 (s, 1H), 7.27 - 7.48 (m, 6H), 7.76 (d, 1H), 8.58 (s, 1H).

Example 67A

Methyl ({10-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-8-cyano-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepin-1-yl}oxy)acetate



Preparation takes place in analogy to Example 64A from 186 mg (0.57 mmol) of the compound from Example 39A and 120 mg (0.69 mmol) of 5-tert-butyl-

3-(chloromethyl)-1,2,4-oxadiazole. The crude product is separated by preparative HPLC (method 11). 28 mg (10% of theory) of the desired product are obtained.

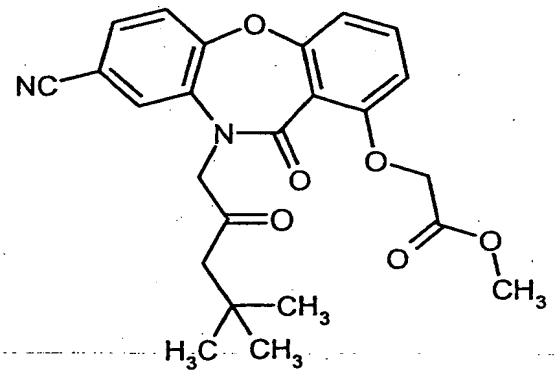
LC-MS (method 4): R_t = 3.01 min,

MS (ESI): m/z = 463 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.35 (s, 9H), 3.63 (s, 3H), 4.82 (d, 1H), 4.87 (d, 1H), 5.31 (d, 1H), 5.49 (d, 1H), 6.87 (d, 1H), 7.04 (d, 1H), 7.45 (dd, 1H), 7.60 (d, 1H), 7.73 (d, 1H), 8.31 (s, 1H).

Example 68A

Methyl {[8-cyano-10-(4,4-dimethyl-2-oxopentyl)-11-oxo-10,11-dihydrodibenzo-[*b*,*f*][1,4]oxazepin-1-yl]oxy}acetate



Preparation takes place in analogy to Example 64A from 224 mg (0.69 mmol) of the compound from Example 39A and 171 mg (0.83 mmol) of 1-bromo-4,4-dimethyl-2-pentanone. The crude product is chromatographed on silica gel (cyclohexane:ethyl acetate 5:1). 111 mg (37% of theory) of the desired product are obtained.

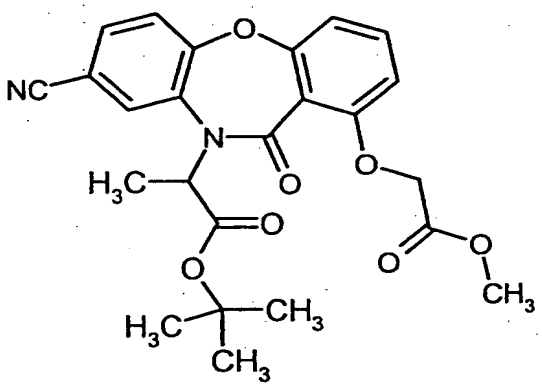
LC-MS (method 10): R_t = 2.37 min,

MS (ESI): m/z = 437 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 0.98 (s, 9H), 2.36 (d, 1H), 2.43 (d, 1H), 3.67 (s, 3H), 4.81 (s, 2H), 4.91 (s, 2H), 6.87 (d, 1H), 7.04 (d, 1H), 7.45 (dd, 1H), 7.57 (d, 1H), 7.71 (s, 1H), 7.87 (d, 1H).

Example 69A

tert-Butyl (R,S)-2-[8-cyano-1-(2-methoxy-2-oxoethoxy)-11-oxodibenzo[b,f][1,4]-oxazepin-10(11H)-yl]propionate



A solution of 267 mg (0.82 mmol) of the compound from Example 39A and 206 mg (0.99 mmol) of methyl 2-bromopropionate in 20 ml of DMF is mixed with 227 mg (1.65 mmol) of potassium carbonate and stirred at RT overnight. A further 3 equivalents each of potassium carbonate and methyl 2-bromopropionate are added, and the mixture is again stirred at RT overnight. 20 ml of 1M hydrochloric acid are added, and the mixture is extracted with ethyl acetate. The combined extracts are dried over magnesium sulphate and concentrated in vacuo. The crude product is chromatographed on silica gel (cyclohexane:ethyl acetate 3:1). 250 mg (67% of theory) of the product are obtained.

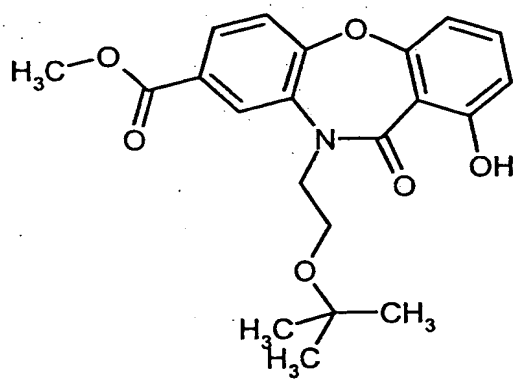
LC-MS (method 10): R_t = 2.32 min,

MS (ESI): m/z = 475 $(M+Na)^+$.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 1.63 + 1.67 (2xd, 3H), 3.66 (s, 3H), 4.62 + 4.89 (2xq, 1H), 4.82 (s, 2H), 6.88 (d, 1H), 7.03 (d, 1H), 7.45 (dd, 1H), 7.59 (m, 1H), 7.75 (m, 1H), 7.90 + 7.95 (2xs, 1H).

Example 70A

Methyl 10-(2-tert-butoxyethyl)-1-hydroxy-11-oxo-10,11-dihydrodibenzo[*b,f*][1,4]-oxazepine-8-carboxylate



A solution of 394 mg (0.83 mmol) of the compound from Example 64A in 15 ml of ethanol is mixed with 66 mg of 10% palladium on activated carbon. The suspension is left to stir in a hydrogen atmosphere under atmospheric pressure for 20 h. It is then filtered through kieselguhr, washed with 20 ml of ethanol and concentrated in vacuo. 227 mg (68% of theory) of the desired product are obtained.

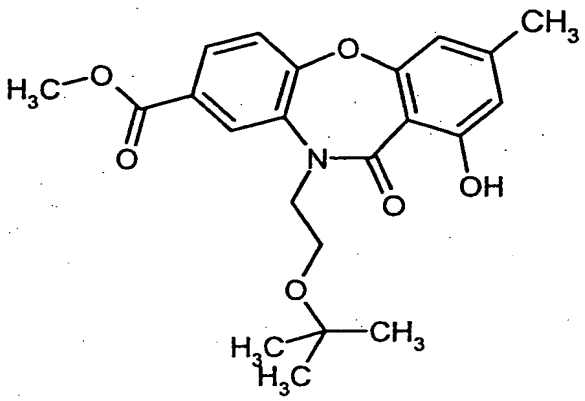
LC-MS (method 7): R_t = 3.69 min,

MS (ESI): m/z = 386 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.10 (s, 9H), 3.71 (m, 2H), 3.85 (s, 3H), 4.07 (m, 2H), 6.75 (d, 1H), 6.82 (d, 1H), 7.35 (dd, 1H), 7.46 (d, 1H), 7.80 (d, 1H), 8.51 (s, 1H), 10.3 (s, br, 1H).

Example 71A

Methyl 10-(2-tert-butoxyethyl)-1-hydroxy-3-methyl-11-oxo-10,11-dihydrodibenzo-[*b*,*f*][1,4]oxazepine-8-carboxylate



A solution of 265 mg (0.54 mmol) of the compound from Example 66A in 24 ml of a 1:1 mixture of ethanol and ethyl acetate is mixed with 58 mg of 10% palladium on activated carbon and 205 mg (3.3 mmol) of ammonium formate. The mixture is stirred at the reflux temperature for 2 h. After cooling to RT, it is filtered through Celite and washed with ethanol. Condensing out the volatile constituents is followed by taking up in ethyl acetate and washing several times with water. The organic phase is dried over magnesium sulphate and concentrated in vacuo. 222 mg (99% of theory) of the desired product are obtained.

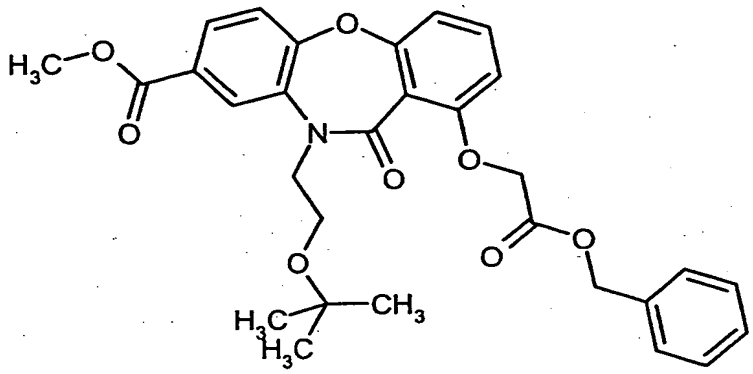
LC-MS (method 4): R_t = 3.38 min,

MS (ESI): m/z = 400 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.08 (s, 9H), 2.23 (s, 3H), 3.71 (m, 2H), 3.83 (s, 3H), 4.10 (m, 2H), 6.61 (s, 1H), 6.68 (s, 1H), 7.43 (d, 1H), 7.82 (d, 1H), 8.49 (s, 1H), 10.3 (s, br, 1H).

Example 72A

Methyl 1-[2-(benzyloxy)-2-oxoethoxy]-10-(2-tert-butoxyethyl)-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine-8-carboxylate



Preparation takes place in analogy to Example 7A from 211 mg (0.55 mmol) of the compound from Example 70A and 125 mg (0.55 mmol) of benzyl bromoacetate. Purification by chromatography on silica gel (dichloromethane:methanol 1:0 to 3:1) results in 279 mg (85% of theory) of the product.

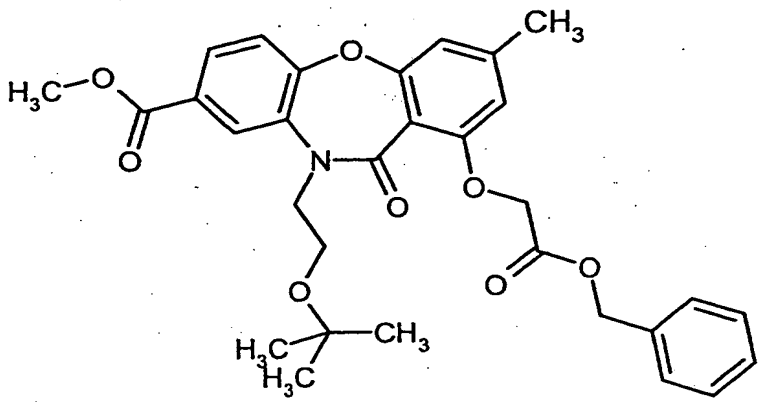
LC-MS (method 2): R_t = 4.08 min,

MS (ESI): m/z = 534 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.07 (s, 9H), 3.53 (m, 2H), 3.75 (m, 1H), 3.82 (s, 3H), 4.37 (m, 1H), 4.86 (d, 1H), 4.91 (d, 1H), 5.12 (s, 2H), 6.86 (d, 1H), 7.00 (d, 1H), 7.27 (s, 5H), 7.38 (dd, 1H), 7.46 (d, 1H), 7.76 (d, 1H), 8.52 (s, 1H).

Example 73A

Methyl 1-[2-(benzyloxy)-2-oxoethoxy]-10-(2-tert-butoxyethyl)-3-methyl-11-oxo-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine-8-carboxylate



Preparation takes place in analogy to Example 7A from 93 mg (0.48 mmol) of the compound from Example 71A and 140 mg (0.58 mmol) of benzyl bromoacetate. Purification by chromatography on a silica gel column (dichloromethane:methanol 1:0 to 3:1) results in 241 mg (92% of theory) of the product.

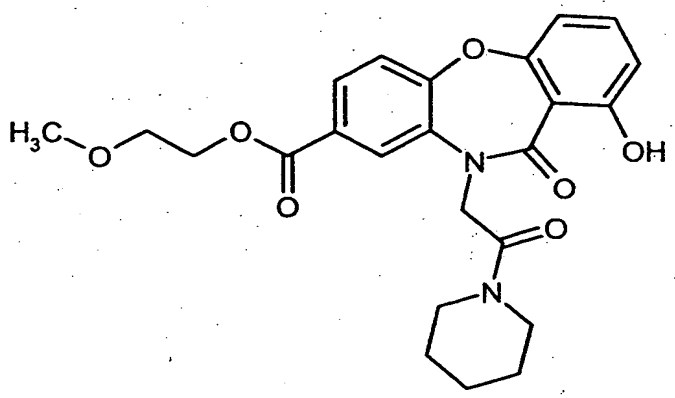
LC-MS (method 7): R_t = 3.72 min,

MS (ESI): m/z = 548 $(M+H)^+$:

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.07 (s, 9H), 2.23 (s, 3H), 3.55 (m, 2H), 3.75 (m, 1H), 3.83 (s, 3H), 4.25 (m, 1H), 4.87 (s, 2H), 5.12 (s, 2H), 6.65 (s, 1H), 6.83 (s, 1H), 7.29 (s, 5H), 7.39 (dd, 1H), 7.41 (d, 1H), 7.76 (d, 1H), 8.52 (s, 1H).

Example 74A

2-Methoxyethyl 1-hydroxy-11-oxo-10-[2-oxo-2-(1-piperidinyl)ethyl]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



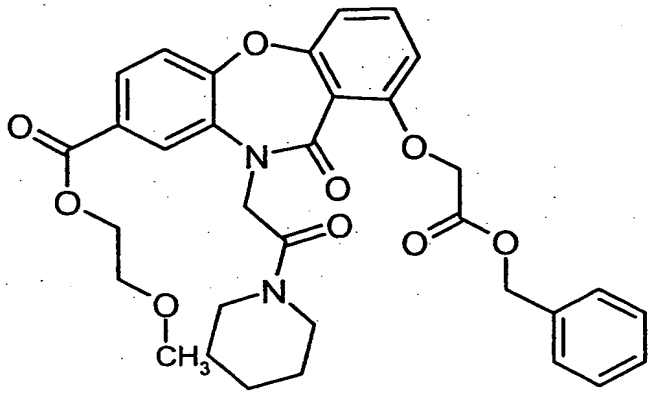
150 mg (0.46 mmol) of 2-methoxyethyl 1-hydroxy-11-oxo-10,11-dihydrodibenzo-[b,f][1,4]oxazepine-8-carboxylate are dissolved in 6 ml of DMF at RT, and 0.097 ml (0.46 mmol) of 1-(bromoacetyl)piperidine and 126 mg (0.91 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 minutes and then at 50°C overnight. The reaction solution is worked up by dilution with 1 ml of water and purification by preparative HPLC (method 11). 66 mg (27% of theory) of the product are obtained.

LC-MS (method 7): $R_t = 3.59$ min

MS (ESIpos): m/z = 455 $(M+H)^+$

Example 75A

2-Methoxyethyl 1-[2-(benzyloxy)-2-oxoethoxy]-11-oxo-10-[2-oxo-2-(1-piperidinyl)-ethyl]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate



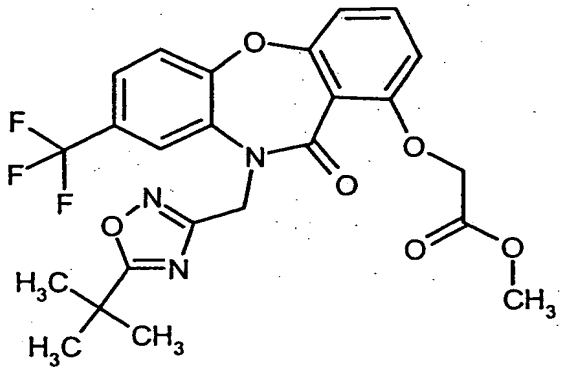
62 mg (0.12 mmol; 87% pure) of 2-methoxyethyl 1-hydroxy-11-oxo-10-[2-oxo-2-(1-piperidinyl)ethyl]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 6 ml of DMF at RT, and 0.042 ml (0.18 mmol) of benzyl bromoacetate and 33 mg (0.24 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 50°C overnight. The mixture is worked up by diluting with 1 ml of water and purifying by preparative HPLC (method 11). 55.0 mg (71% of theory) of the product are obtained.

LC-MS (method 4): $R_t = 4.30$ min

MS (ESIpos): $m/z = 603$ $(M+H)^+$

Example 76A

Methyl {[10-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetate



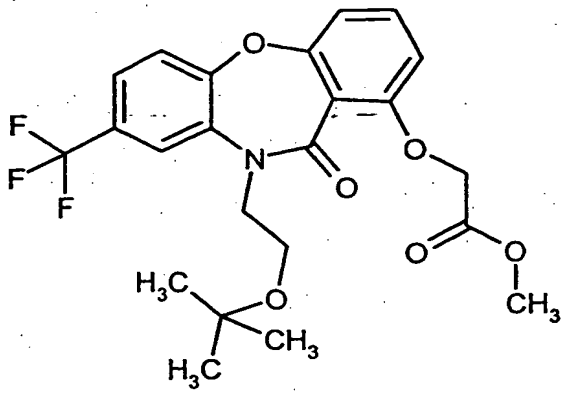
94 mg (0.26 mmol) of methyl {[11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo-[b,f][1,4]oxazepin-1-yl]oxy}acetate are dissolved in 5 ml of DMF at RT, and 89 mg (0.51 mmol) of 5-tert-butyl-3-(chloromethyl)-1,2,4-oxadiazole and 71 mg (0.51 mmol) of potassium carbonate are added. The mixture is stirred at RT for 10 min and then at 50°C for 2 hours. The mixture is worked up by diluting with water/acetonitrile and purifying by preparative HPLC (method 11). 103 mg (79% of theory) of the product are obtained.

LC-MS (method 4): R_t = 3.90 min

MS (ESIpos): m/z = 506 $(M+H)^+$

Example 77A

Methyl {[10-(2-tert-butoxyethyl)-11-oxo-8-(trifluoromethyl)-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetate



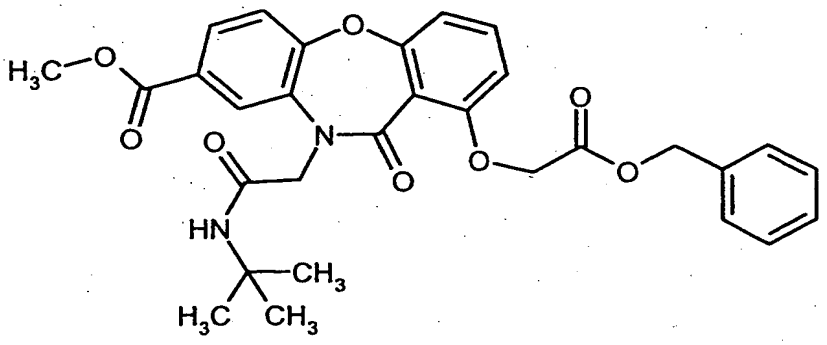
94 mg (0.26 mmol) of methyl {[11-oxo-8-(trifluoromethyl)-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetate are dissolved in a mixture of 0.2 ml of DMF and 4.0 ml of dioxane at RT, and 71 mg (0.51 mmol) of potassium carbonate and 8.5 mg (0.05 mmol) of potassium iodide are added. The mixture is stirred at 60°C for 1 hour and then 93 mg (0.51 mmol) of 2-(2-bromoethoxy)-2-methylpropane are added. The mixture is stirred at 100°C overnight and then a further 93 mg (0.51 mmol) of 2-(2-bromoethoxy)-2-methylpropane are added, and the mixture is again stirred at 100°C overnight. For working up, the reaction solution is purified by preparative HPLC (method 11). 33.0 mg (27% of theory) of the product are obtained.

LC-MS (method 4): R_t = 4.00 min

MS (ESIpos): m/z = 468 $(M+H)^+$

Example 78A

{[10-[2-(tert-Butylamino)-2-oxoethyl]-8-(methoxycarbonyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



10 mg (0.14 mmol) of tert-butylamine and 4.4 mg (0.035 mmol) of dimethylamino-pyridine and 20 mg (0.11 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride are added to 35 mg (0.071 mmol) of the compound from Example 9A in 3 ml of dichloromethane. After stirring at room temperature overnight, the solvent is removed under reduced pressure, and the residue is purified by preparative HPLC (method 11) to give 14 mg (37% of theory) of product.

LC-MS (method 2): R_t = 3.9 min,

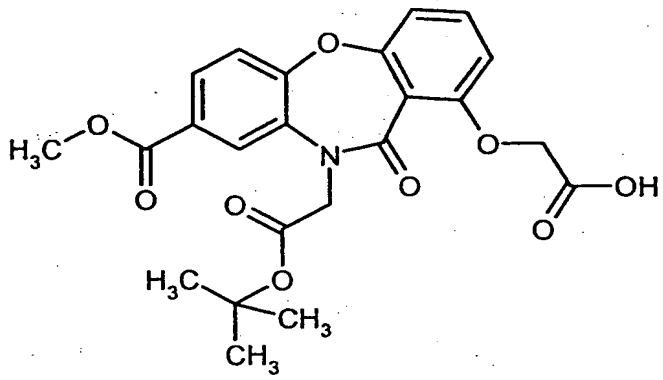
MS (ESI): m/z = 547 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.27 (s, 9H), 3.85 (s, 3H), 4.65 (AB signal, 2H), 4.90 (AB signal, 2H), 5.17 (s, 2H), 6.89 (s, 1H), 7.05 (s, 1H), 7.32 (s, 4H), 7.44 (dd, 1H), 7.50 (d, 1H), 7.77-7.82 (m, 2H), 7.96 (d, 1H).

Exemplary embodiments:

Example 1

{[10-(2-tert-Butoxy-2-oxoethyl)-8-(methoxycarbonyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



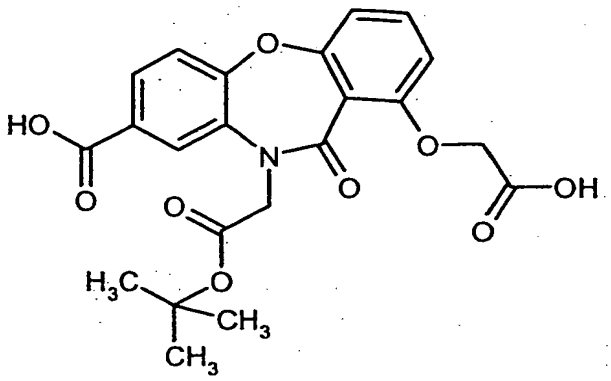
2.1 mg of trimethylsilyl chloride (0.020 mmol) and 2.9 mg of sodium iodide (0.020 mmol) are added to 0.10 g (0.19 mmol) of the compound from Example 5A in 3 ml of chloroform, and the mixture is heated under reflux overnight. The mixture is diluted with 20 ml of ethyl acetate and extracted three times with 20 ml of 1N hydrochloric acid each time. The organic phase is dried over magnesium sulphate. Removal of the solvent under reduced pressure results in a residue which is purified by preparative HPLC (method 11) to give 75 mg (84% of theory) of product.

MS (ESI): m/z = 458 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.38 (s, 9H), 3.84 (s, 3H), 4.56 (s, 2H), 4.68 (s, 2H), 6.80 (d, 1H), 6.97 (d, 1H), 7.42 (t, 1H), 7.50 (d, 1H), 7.80 (dd, 1H), 7.96 (d, 1H).

Example 2

10-(2-tert-Butoxy-2-oxoethyl)-1-(carboxymethoxy)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepine-8-carboxylic acid



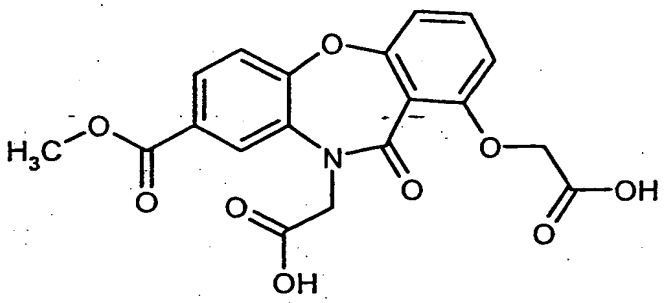
0.27 g (0.53 mmol) of the compound from Example 5A in 2.5 ml of methanol is mixed with 30 mg (0.53 mmol) of potassium hydroxide and stirred at room temperature for 4 h. The mixture is poured into 15 ml of ethyl acetate and extracted three times with 20 ml of 1N sodium hydroxide solution each time. The aqueous phases are acidified with conc. hydrochloric acid and extracted three times with 20 ml of ethyl acetate each time. The organic phases are dried over magnesium sulphate. Removal of the solvent under reduced pressure results in 0.17 g (65% of theory) of product.

MS (ESI): m/z = 444 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.38 (2, 9H), 4.64-4.74 (m, 4H), 6.84 (d, 1H), 7.01 (d, 1H), 7.40-7.51 (m, 2H), 7.79 (dd, 1H), 7.95 (d, 1H), 13.0 (br. s, 2H).

Example 3

[1-(Carboxymethoxy)-8-(methoxycarbonyl)-11-oxodibenzo[b,f][1,4]oxazepin-10(11H)-yl]acetic acid



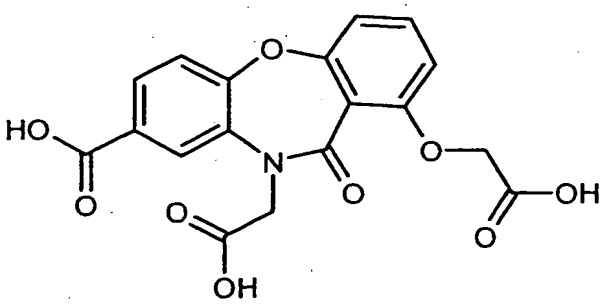
0.10 g (0.19 mmol) of the compound from Example 5A in 3 ml of methylene chloride is mixed with 60 µl (88 mg, 0.78 mmol) of trifluoroacetic acid and stirred at room temperature for two days. The mixture is poured into 15 ml of ethyl acetate and extracted three times with 20 ml of 1N hydrochloric acid each time. The organic phase is dried over magnesium sulphate. Removal of the solvent under reduced pressure results in a residue which is purified by preparative HPLC (method 11) to give 26 mg (32% of theory) of product.

MS (ESI): m/z = 402 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.84 (s, 3H), 4.55-4.85 (m, 4H), 6.83, (d, 1H), 7.01 (d, 1H), 7.45 (dd, 1H), 7.50 (d, 1H), 7.81 (dd, 1H), 7.98 (d, 1H), 13.0 (br. s, 2 H).

Example 4

1-(Carboxymethoxy)-10-(carboxymethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepine-8-carboxylic acid



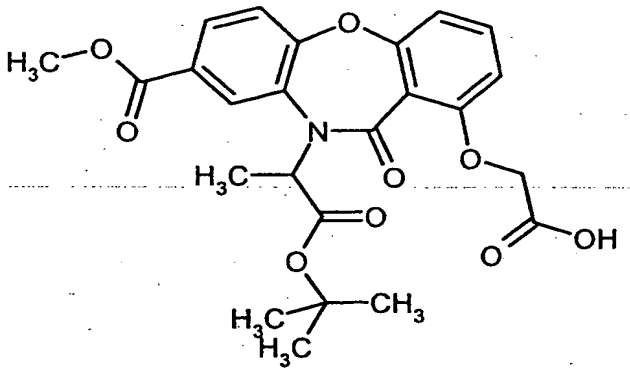
50 mg (0.10 mmol) of the compound from Example 5A in 1 ml of dioxane and 300 µl of water are mixed with 11 mg (0.19 mmol) of potassium hydroxide and stirred at room temperature overnight. The mixture is poured into 10 ml of ethyl acetate and extracted three times with 10 ml of 1N hydrochloric acid each time. The organic phase is dried over magnesium sulphate. The solvent is removed under reduced pressure. The residue is purified by preparative HPLC (method 11), and 12 mg (29% of theory) of product are obtained.

MS (ESI): m/z = 388 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 4.5-4.8 (m, 4H), 6.83 (d, 1H), 7.00 (d, 1H), 7.41-7.49 (m, 2H), 7.78 (dd, 1H), 7.95 (d, 1H), 13.1 (br. s, 3H).

Example 5

(R,S)-{[10-(2-tert-Butoxy-1-methyl-2-oxoethyl)-8-(methoxycarbonyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



A solution of 16 mg (0.03 mmol) of the compound from Example 7A in 1 ml of THF is mixed under argon with 1.5 mg of 10% palladium on activated carbon and stirred in a hydrogen atmosphere for 2 h. The mixture is filtered through Celite, washing with ethyl acetate, and concentrated in vacuo. 10 mg (71% of theory) of the product are obtained.

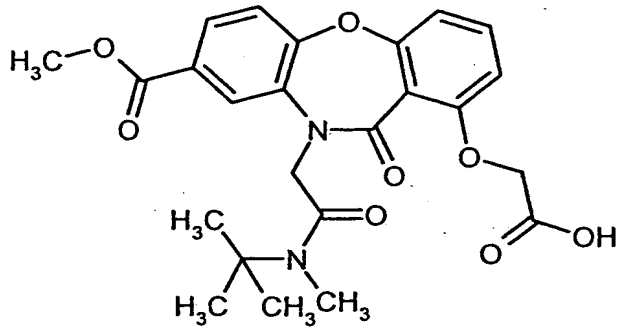
LC-MS (method 2): R_t = 3.7 min,

MS (ESI): m/z = 472 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.36, 1.40 (2xs, 9H), 1.48, 1.52 (2xd, 3H), 3.83 (s, 3H), 4.70 (s, 2H), 4.89 (m, 1H), 6.82 (dd, 1H), 7.00 (d, 1H), 7.42 (dd, 1H), 7.51 (d, 1H), 7.82 (d, 1H), 7.85 (s, 1H), 13.05 (s_{br}, 1H).

Example 6

{[10-{2-[tert-Butyl(methyl)amino]-2-oxoethyl}-8-(methoxycarbonyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



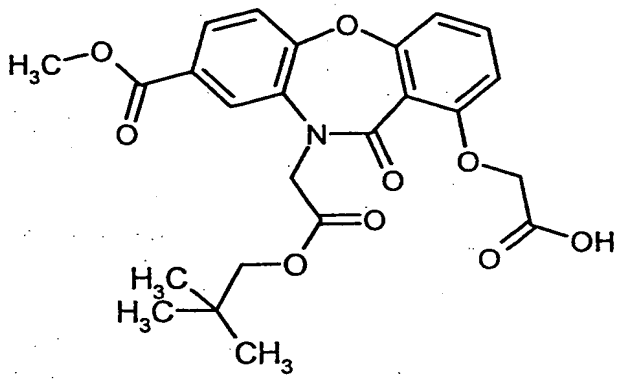
A solid is obtained from 75 mg (0.13 mmol) of the compound from Example 10A by the process described for Example 5 and is crystallized from dichloromethane/diethyl ether. 28 mg (45% of theory) of the product are obtained.

LC-MS (method 3): R_t = 3.47 min,

MS (ESI): m/z = 471 $(M+H)^+$.

Example 7

({8-(Methoxycarbonyl)-10-[2-(neopentyloxy)-2-oxoethyl]-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl}oxy)acetic acid

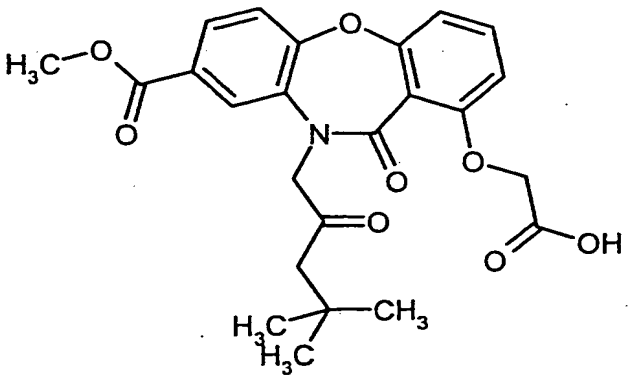


A solid is obtained from 60 mg (0.11 mmol) of the compound from Example 11A by the process described for Example 5 and is crystallized from diethyl ether. 30 mg (60% of theory) of the product are obtained.

LC-MS (method 3): R_t = 3.70 min,
MS (ESI): m/z = 472 $(M+H)^+$.

Example 8

{[10-(4,4-Dimethyl-2-oxopentyl)-8-(methoxycarbonyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



A solution of 284 mg (0.52 mmol) of the compound from Example 13A in 26 ml of ethyl acetate:ethanol 1:1 is mixed under argon with 197 mg (3.1 mmol) of ammonium formate and 111 mg of 10% palladium on activated carbon. The mixture is stirred at an oil bath temperature of 80°C for 3 h, allowed to cool to RT and filtered through Celite. The filtrate is diluted with ethyl acetate and washed with 0.1M hydrochloric acid. The combined organic phases are dried over magnesium sulphate and concentrated in vacuo. 222 mg (80% of theory) of the desired product are obtained.

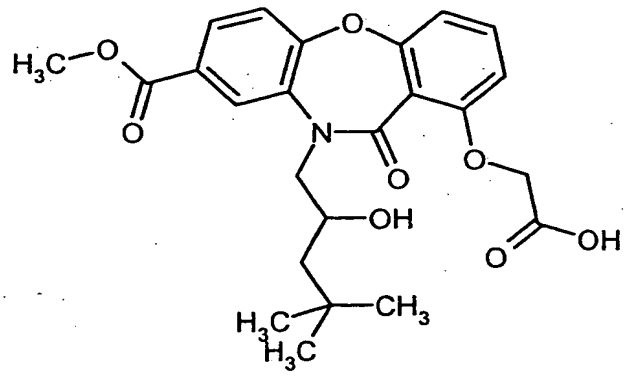
LC-MS (method 3): R_t = 3.59 min,

MS (ESI): m/z = 456 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.02 (s, 9H), 2.38 (d, 1H), 2.52 (d, 1H), 3.82 (s, 3H), 4.69 (s, 2H), 4.78 (d, 1H), 4.99 (d, 1H), 6.81 (d, 1H), 7.01 (d, 1H), 7.45 (dd, 1H), 7.50 (d, 1H), 7.79 (m, 2H), 12.97 (s, br, 1H).

Example 9

(R,S)-1-{[10-(2-(4,4-Dimethyl-2-hydroxypentyl)-2-oxoethyl)-8-(methoxycarbonyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



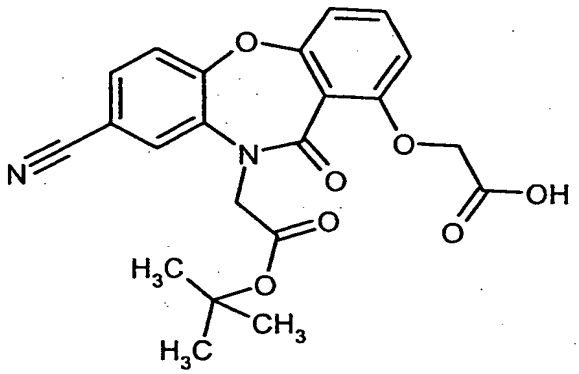
35 mg of sodium borohydride are added in portions over the course of 24 h to a solution of 50 mg (0.11 mmol) of the compound from Example 8 in 2 ml of

methanol. After the reaction is complete, 20 ml of ethyl acetate are added, the solution is washed with water, and the combined organic extracts are dried with magnesium sulphate. After removal of the volatile constituents in vacuo, the residue is chromatographed on silica gel (ethyl acetate:cyclohexane 1:1). 18 mg (35% of theory) of the desired product are obtained.

LC-MS (method 3): R_t = 3.25 min,
MS (ESI): m/z = 458 $(M+H)^+$.

Example 10

{[10-(2-tert-Butoxy-2-oxoethyl)-8-cyano-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepin-1-yl]oxy}acetic acid



100 mg (0.21 mmol) of tert-butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-cyano-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate are dissolved in 5 ml of trichloromethane at RT, and 22 mg (0.21 mmol) of chlorotrimethylsilane and 31 mg (0.21 mmol) of sodium iodide are added. The mixture is stirred under reflux overnight. Cooling is followed by dilution with methylene chloride and addition of 1 ml of 1N hydrochloric acid. The reaction mixture is concentrated in vacuo. The residue is dissolved in DMSO and purified by preparative HPLC (method 11). 36 mg (40 % of theory) of the product are obtained.

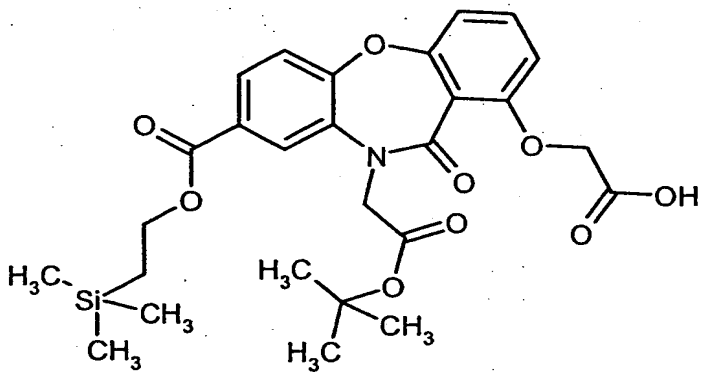
LC-MS (method 7): R_t = 3.41 min

MS (ESIpos): m/z = 425 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.34 (s, 9H), 4.49-4.88 (m, 4 H), 6.86 (d, 1 H), 7.02 (d, 1 H), 7.46 (t, 1 H), 7.58 (d, 1 H), 7.73 (d, 1H), 8.01 (s, 1H), 13.00 (s_{br}, 1 H).

Example 11

[(10-(2-tert-Butoxy-2-oxoethyl)-11-oxo-8-{[2-(trimethylsilyl)ethoxy]carbonyl}-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl)oxy]acetic acid



70 mg (0.12 mmol) of 2-(trimethylsilyl)ethyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 3 ml of trichloromethane at RT, and 13 mg (0.12 mmol) of chlorotrimethylsilane and 17 mg (0.12 mmol) of sodium iodide are added. The mixture is stirred under reflux for 3 hours. Cooling is followed by dilution with methylene chloride and addition of 1 ml of 1N hydrochloric acid. The reaction mixture is concentrated in vacuo. The residue is dissolved in DMSO and purified by preparative HPLC (method 11). 36 mg (56% of theory) of the product are obtained.

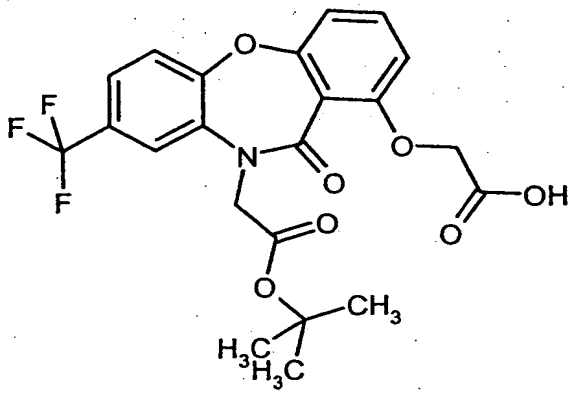
LC-MS (method 7): R_t = 4.26 min

MS (ESIpos): m/z = 544 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.01 (s, 9 H), 1.01 (t, 2H), 1.35 (s, 9H), 4.31 (t, 2H), 4.49-4.71 (m, 4 H), 6.80 (d, 1 H), 6.96 (d, 1 H), 7.36-7.48 (m, 2 H), 7.74 (dd, 1 H), 7.89 (s, 1H), 12.94 (s_{br}, 1 H).

Example 12

{[10-(2-tert-Butoxy-2-oxoethyl)-11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo-[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



200 mg (0.38 mmol) of tert-butyl [1-(2-tert-butoxy-2-oxoethoxy)-11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate are dissolved in 5 ml of trichloromethane at RT and, under argon, 42 mg (0.38 mmol) of chlorotrimethylsilane and 57 mg (0.38 mmol) of sodium iodide are added. The mixture is stirred under reflux overnight. Cooling is followed by dilution with methylene chloride and addition of 1 ml of ammonium chloride solution. The reaction mixture is concentrated in vacuo. The residue is dissolved in acetonitrile and purified by preparative HPLC (method 11). 130 mg (72% of theory) of the product are obtained.

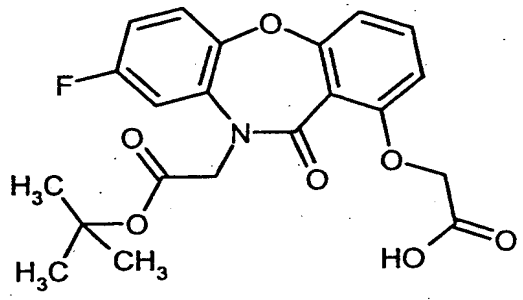
LC-MS (method 4): R_t = 4.20 min

MS (ESIpos): m/z = 468 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.35 (s, 9 H), 4.59-4.84 (m, 4 H), 6.86 (d, 1 H), 7.03 (d, 1 H), 7.45 (t, 2 H), 7.60 (s, 2 H), 7.84 (s, 1H), 13.00 (s_{br}, 1 H)

Example 13

{[10-(2-tert-Butoxy-2-oxoethyl)-8-fluoro-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepin-1-yl]oxy}acetic acid



150 mg (0.32 mmol) of tert-butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-fluoro-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate are dissolved in 5 ml of anhydrous chloroform and, after addition of 10.3 mg (0.1 mmol) of chlorotrimethylsilane and 14.3 mg (0.1 mmol) of sodium iodide, stirred under reflux overnight. The mixture is then diluted with dichloromethane and washed once with 1N hydrochloric acid. The organic phase is dried over magnesium sulphate, filtered and concentrated. Purification takes place by preparative HPLC (method 11). This results in 57.8 mg (43% of theory) of product.

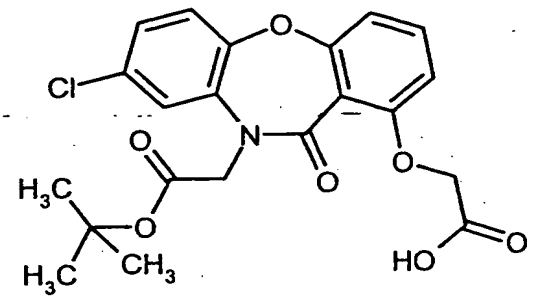
HPLC (method 8): $R_t = 4.52$ min

MS (DCI): m/z = 418 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 9 H), 4.31 (d, 1 H), 4.79 (s, 2 H), 4.81 (d, 1 H), 6.84 (d, 1 H), 6.89-7.00 (m, 3 H), 7.23 (m, 1 H), 7.45 (t, 1 H), 12.62 (s_{br}, 1 H)

Example 14

{[10-(2-tert-Butoxy-2-oxoethyl)-8-chloro-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepin-1-yl]oxy}acetic acid



200 mg (0.41 mmol) of tert-butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-chloro-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate are dissolved in 5 ml of anhydrous chloroform and, after addition of 22.2 mg (0.2 mmol) of chlorotrimethylsilane and 30.6 mg (0.2 mmol) of sodium iodide, stirred under reflux for 7 hours. The mixture is then diluted with dichloromethane and washed once with 1N hydrochloric acid. The organic phase is dried over magnesium sulphate, filtered and concentrated. Purification takes place by preparative HPLC (method 11). This results in 90 mg (51% of theory) of product.

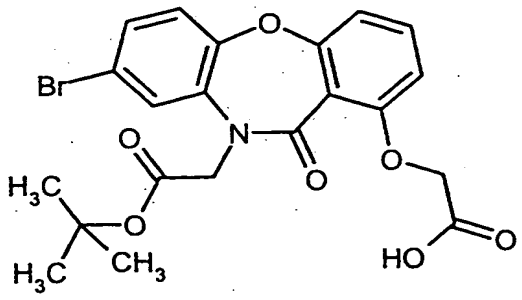
HPLC (method 8): R_t = 4.62 min

MS (DCI): m/z = 434 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H), 4.34 (d, 1 H), 4.76-4.78 (m, 3 H), 6.84 (d, 1 H), 6.95 (dd, 1 H), 7.18-7.23 (m, 3 H), 7.44 (t, 1 H), 12.6 (s_{br}, 1 H)

Example 15

[8-Bromo-1-(2-tert-butoxy-2-oxoethoxy)-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetic acid



100 mg (0.19 mmol) of tert-butyl [8-bromo-1-(2-tert-butoxy-2-oxoethoxy)-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate are dissolved in 2 ml of anhydrous chloroform and, after addition of 2.1 mg (0.02 mmol) of chlorotrimethylsilane and 28 mg (0.19 mmol) of sodium iodide, are stirred under reflux for 7 hours. The mixture is then diluted with dichloromethane and washed once with 1N hydrochloric acid. The organic phase is dried over magnesium sulphate, filtered and concentrated. Purification takes place by preparative HPLC (method 11). This results in 48 mg (53% of theory) of product.

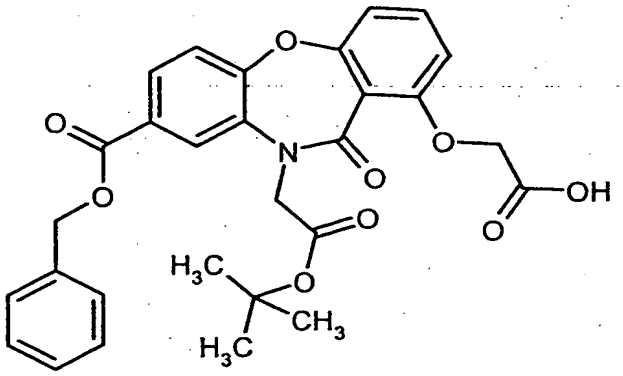
HPLC (method 9): R_t = 4.74 min

MS (DCI): m/z = 478 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 4.59 (d, 1 H), 4.71-4.79 (m, 3 H), 6.83 (d, 1 H), 6.98 (d, 1 H), 7.31-7.48 (m, 3 H), 7.69 (d, 1 H), 13.06 (s_{br}, 1 H)

Example 16

{[8-[(Benzyloxy)carbonyl]-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



100 mg (0.17 mmol) of benzyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 3 ml of trichloromethane at RT, and 18 mg (0.17 mmol) of chlorotrimethylsilane and 25 mg (0.17 mmol) of sodium iodide are added. The

mixture is stirred under reflux for 4 hours. Cooling is followed by dilution with methylene chloride and addition of 1 ml of 1N hydrochloric acid. The reaction mixture is concentrated in vacuo. The residue is dissolved in acetonitrile and purified by preparative HPLC (method 11). 36 mg (56% of theory) of the product are obtained.

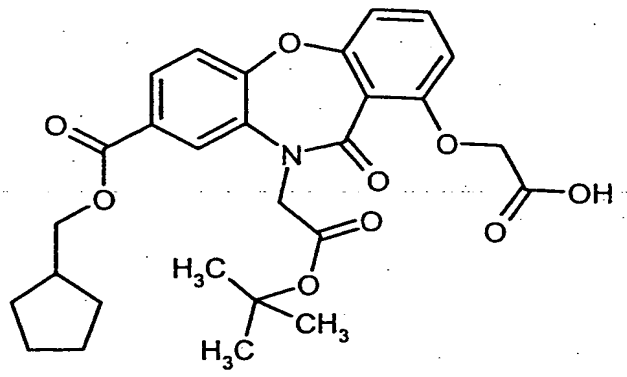
LC-MS (method 3): R_t = 4.17 min

MS (ESIpos): m/z = 534 $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.35 (s, 19H), 4.50-4.76 (m, 4H), 5.33 (dd, 2H), 6.83 (d, 1 H), 7.01 (d, 1 H), 7.31-7.54 (m, 7 H), 7.85 (dd, 1 H), 7.98 (d, 1H), 13.08 (s_{br}, 1 H).

Example 17

({10-(2-tert-Butoxy-2-oxoethyl)-8-[(cyclopentylmethoxy)carbonyl]-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl}oxy)acetic acid



150 mg (0.26 mmol) of cyclopentylmethyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 3 ml of trichloromethane at RT, and 28 mg (0.26 mmol) of chlorotrimethylsilane and 39 mg (0.26 mmol) of sodium iodide are added. The mixture is stirred under reflux for 2 hours. Cooling is followed by dilution with methylene chloride and addition of 1 ml of 1N hydrochloric acid. The reaction mixture is

concentrated in vacuo. The residue is dissolved in acetonitrile and purified by preparative HPLC (method 11). 104 mg (76% of theory) of the product are obtained.

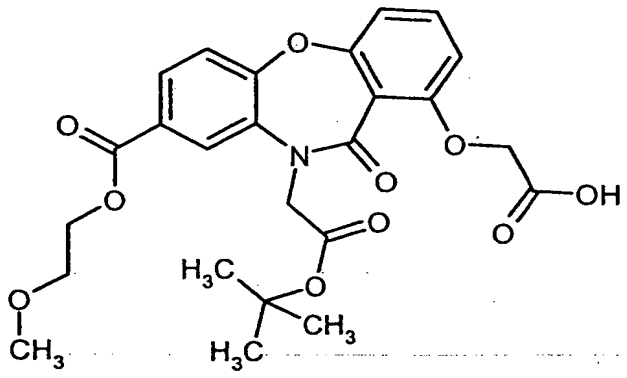
LC-MS (method 7): R_t = 4.13 min

MS (ESIpos): m/z = 526 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.12-1.81 (m, 17H), 2.19-2.43 (m, 1h), 4.15 (t, 2H), 4.52-4.79 (m, 4 H), 4.52- 4.74 (m, 4H), 6.84 (d, 1 H), 7.01 (d, 1 H), 7.42-7.52 (m, 2 H), 7.79 (dd, 1 H), 7.82 (d, 1H), 12.98 (s_{br}, 1 H).

Example 18

({10-(2-tert-Butoxy-2-oxoethyl)-8-[(2-methoxyethoxy)carbonyl]-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl}oxy)acetic acid



100 mg (0.18 mmol) of 2-methoxyethyl 1-(2-tert-butoxy-2-oxoethoxy)-10-(2-tert-butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 3 ml of trichloromethane at RT, and 19 mg (0.18 mmol) of chloro-trimethylsilane and 27 mg (0.18 mmol) of sodium iodide are added. The mixture is stirred under reflux overnight. Cooling is followed by dilution with methylene chloride and addition of 1 ml of 1N hydrochloric acid. The reaction mixture is concentrated in vacuo. The residue is dissolved in acetonitrile and purified by preparative HPLC (method 11). 80 mg (88% of theory) of the product are obtained.

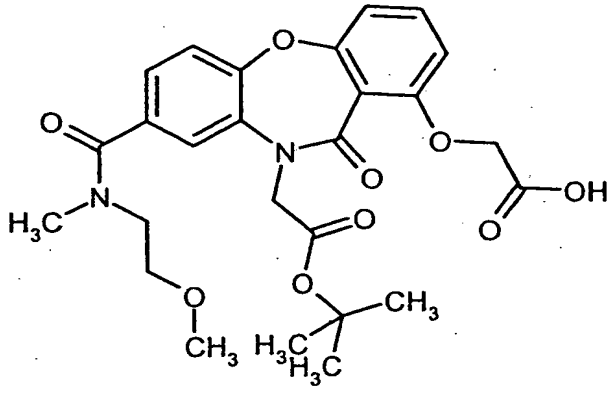
LC-MS (method 7): R_t = 3.47 min

MS (ESIpos): m/z = 502 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.40 (s, 9H), 3.34 (s, 3H), 3.63 (t, 3H), 4.31-4.45 (m, 2 H), 4.52- 4.74 (m, 4H), 6.85 (d, 1 H), 7.01 (d, 1 H), 7.42-7.53 (m, 2 H), 7.80 (dd, 1 H), 7.95 (s, 01), 12.97 (s_{br}, 1 H).

Example 19

[(10-(2-tert-Butoxy-2-oxoethyl)-8-{[(2-methoxyethyl)(methyl)amino]carbonyl}-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl)oxy]acetic acid



150.0 mg (0.263 mmol) of tert-butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-{[(2-methoxyethyl)(methyl)amino]carbonyl}-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]-acetate are dissolved in 6 ml of trichloromethane at RT, and 29 mg (0.26 mmol) of chlorotrimethylsilane and 39 mg (0.26 mmol) of sodium iodide are added. The mixture is stirred under reflux for 4 hours. Cooling is followed by dilution with methylene chloride and addition of 1 ml of water. The reaction mixture is concentrated in vacuo. The residue is dissolved in acetonitrile and purified by preparative HPLC (method 11) (column material: YMC GEL ODS AQ S 5/15 μm; mobile phase: acetonitrile-water gradient 10:90 → 90:10; water + 0.1% hydrochloric acid). Final purification takes place on a silica gel frit (mobile phase: methylene chloride/methanol 5:1). 50 mg (36% of theory) of the product are obtained.

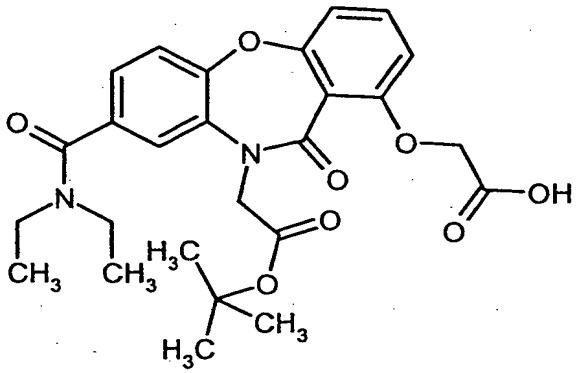
LC-MS (method 7): R_t = 3.19 min

MS (ESIpos): m/z = 515 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.35 (s, 9 H), 2.82-4.79 (m, 10 H), 4.47-4.78 (m, 4 H), 6.78 (d, 1 H), 6.96 (d, 1 H), 7.20 (dd, 1 H), 7.36-7.50 (m, 3 H).

Example 20

({10-(2-tert-Butoxy-2-oxoethyl)-8-[(diethylamino)carbonyl]-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl}oxy)acetic acid



59 mg (0.11 mmol) of tert-butyl [1-(2-tert-butoxy-2-oxoethoxy)-8-[(diethylamino)-carbonyl]-11-oxodibenzo[b,f][1,4]oxazepin-10(11*H*)-yl]acetate are dissolved in 6 ml of trichloromethane at RT, and 12 mg (0.11 mmol) of chlorotrimethylsilane and 16 mg (0.11 mmol) of sodium iodide are added. The mixture is stirred under reflux for 4 hours. Cooling is followed by dilution with methylene chloride and addition of 1 ml of 1N hydrochloric acid. The reaction mixture is concentrated in vacuo. The residue is dissolved in acetonitrile and purified by preparative HPLC (method 11) (mobile phase: acetonitrile-water gradient 10:90 → 90:10; water + 0.1% hydrochloric acid). Final purification takes place on a silica gel frit (mobile phase: methylene chloride/methanol 5:1). 30 mg (56% of theory) of the product are obtained.

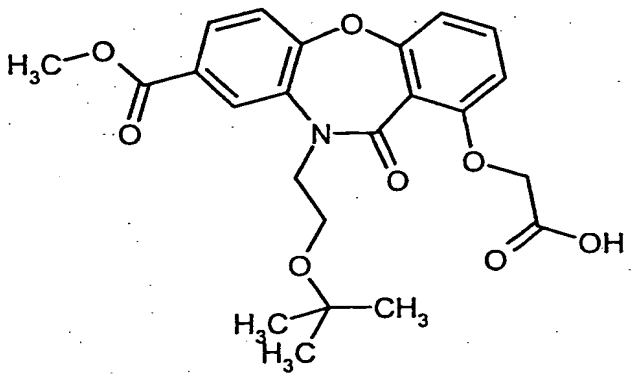
LC-MS (method 7): R_t = 3.40 min

MS (ESIpos): m/z = 499 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.07 (s_{br}, 6 H), 1.34 (s, 9H), 3.21-3.52 (m, 4 H), 4.33 (s, 2 H), 4.60 (d, 1 H), 4.84 (d, 1 H), 6.72 (d, 1 H), 6.90 (d, 1 H), 7.18 (dd, 1 H), 7.30-7.47 (m, 3 H).

Example 21

{[10-(2-tert-Butoxyethyl)-8-(methoxycarbonyl)-11-oxo-10,11-dihydrodibenzo[b,f]-[1,4]oxazepin-1-yl]oxy}acetic acid



Preparation takes place in analogy to Example 8 from 72 mg (0.13 mmol) of the compound from Example 72A. 59 mg (99% of theory) of the desired product are obtained.

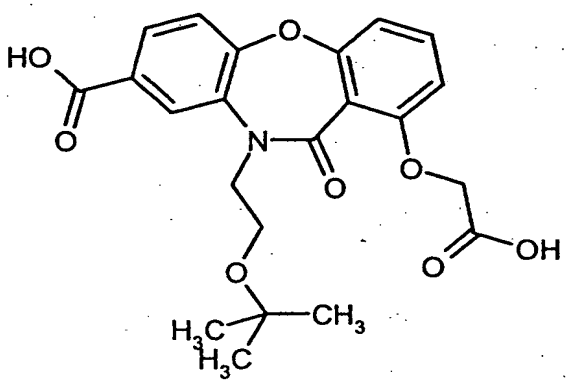
LC-MS (method 2): R_t = 3.60 min,

MS (ESI): m/z = 444 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.08 (s, 9H), 3.58 (m, 1H), 3.77 (m, 1H), 3.82 (s, 3H), 3.85 (m, 1H), 4.20 (m, 1H), 4.62 (s, 2H), 6.68 (d, 1H), 6.88 (d, 1H), 7.35 (dd, 1H), 7.45 (d, 1H), 7.77 (d, 1H), 8.49 (s, 1H).

Example 22

10-(2-tert-Butoxyethyl)-1-(carboxymethoxy)-11-oxo-10,11-dihydrodibenzo-[b,f][1,4]oxazepine-8-carboxylic acid



Preparation takes place in analogy to the method of Example 2 from 28 mg (0.06 mmol) of the compound from Example 21 and 0.09 ml (0.18 mmol) of 2M lithium hydroxide solution. 23 mg (84% of theory) of the desired product are obtained.

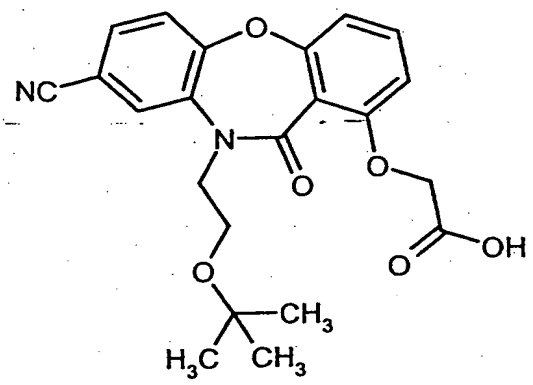
LC-MS (method 7): R_t = 2.69 min,

MS (ESI): m/z = 430 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.08 (s, 9H), 3.55 (m, 1H), 3.72 (m, 1H), 3.88 (m, 1H), 4.21 (m, 1H), 4.71 (s, 2H), 6.83 (d, 1H), 6.99 (d, 1H), 7.41 (dd, 1H), 7.43 (d, 1H), 7.76 (d, 1H), 8.45 (s, 1H), 13.03 (s, br, 1H).

Example 23

{[10-(2-tert-Butoxyethyl)-8-cyano-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid

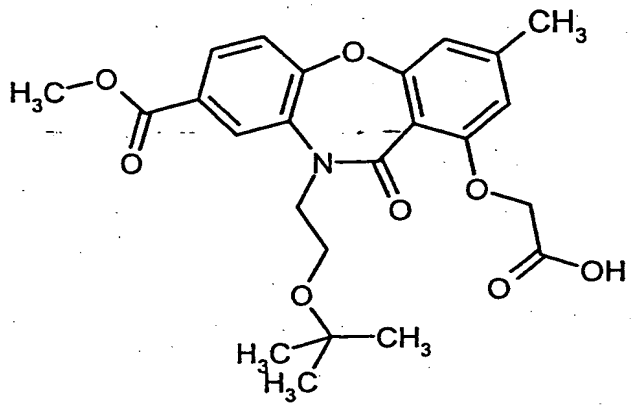


A solution of 49 mg (0.12 mmol) of the compound from Example 65A in 1 ml of THF:methanol 1:1 is mixed with 0.06 ml (0.12 mmol) of a 2M lithium hydroxide solution in water. The mixture is stirred at an oil bath temperature of 60°C for 30 min and diluted with 10 ml of ethyl acetate, and the organic phase is washed with dilute hydrochloric acid and water. It is dried over magnesium sulphate, and the volatile constituents are condensed out in vacuo. 46 mg (98% of theory) of the desired product are obtained.

LC-MS (method 7): $R_t = 3.06$ min,
MS (ESI): $m/z = 411$ $(M+H)^+$.

Example 24

{[10-(2-tert-Butoxyethyl)-8-(methoxycarbonyl)-3-methyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



Preparation takes place in analogy to Example 8 from 270 mg (0.13 mmol) of the compound from Example 73A. 220 mg (95% of theory) of the desired product are obtained.

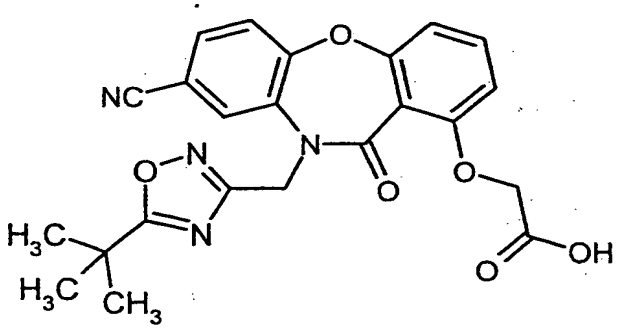
LC-MS (method 2): R_t = 3.77 min,

MS (ESI): m/z = 458 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.10 (s, 9H), 2.28 (s, 3H), 3.57 (m, 1H), 3.75 (m, 1H), 3.81 (m, 1H), 3.83 (s, 3H), 4.22 (m, 1H), 4.68 (s, 2H), 6.66 (s, 1H), 6.81 (s, 1H), 7.42 (d, 1H), 7.68 (d, 1H), 8.53 (s, 1H).

Example 25

({10-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)methyl]-8-cyano-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl}oxy)acetic acid



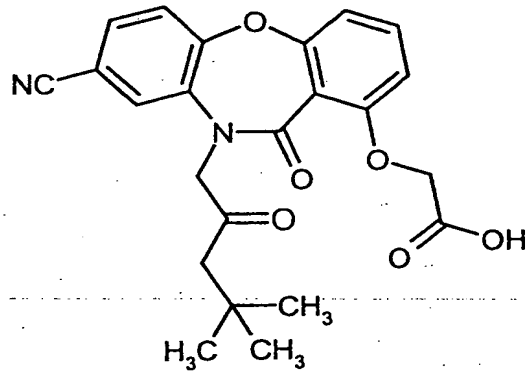
A solution of 23 mg (0.05 mmol) of the compound from Example 67A in 1 ml of dichloromethane is mixed with 8.5 mg (0.06 mmol) of potassium trimethylsilanolate.

The mixture is stirred at RT for 1 h and diluted with 5 ml of dichloromethane, and the organic phase is washed with dilute hydrochloric acid and water. It is dried over magnesium sulphate, and the volatile constituents are condensed out in vacuo. 20 mg (90% of theory) of the desired product are obtained.

LC-MS (method 10): R_t = 2.12 min,
MS (ESI): m/z = 411 $(M+H)^+$.
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.33 (s, 9H), 4.72 (s, 2H), 5.30 (d, 1H), 5.50 (d, 1H), 6.84 (d, 1H), 7.02 (d, 1H), 7.45 (dd, 1H), 7.59 (d, 1H), 7.73 (d, 1H), 8.23 (s, 1H).

Example 26

{[8-Cyano-10-(4,4-dimethyl-2-oxopentyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-oxazepin-1-yl]oxy}acetic acid



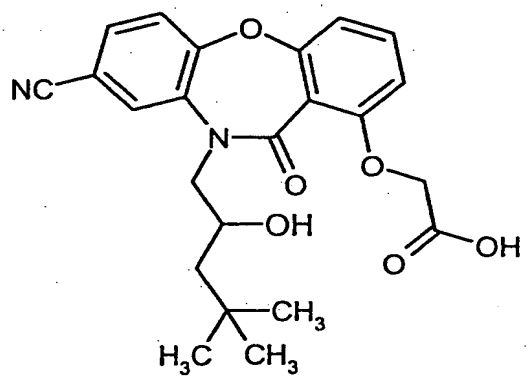
Preparation takes place in analogy to Example 25 from 107 mg (0.25 mmol) of the compound from Example 68A. 81 mg (77% of theory) of the desired product are obtained.

LC-MS (method 10): R_t = 2.18 min,
MS (ESI): m/z = 423 $(M+H)^+$.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 0.98 (s, 9H), 2.37 (d, 1H), 2.46 (d, 1H), 4.58 (s, 2H), 4.87 (d, 1H), 4.97 (d, 1H), 6.79 (d, 1H), 6.97 (d, 1H), 7.42 (dd, 1H), 7.57 (d, 1H), 7.72 (s, 1H), 7.89 (d, 1H).

Example 27

(R,S)-{[8-Cyano-10-(2-hydroxy-4,4-dimethylpentyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



Preparation takes place in analogy to Example 9 from 74 mg (0.18 mmol) of the compound from Example 26. The crude product is purified by preparative HPLC (method 11). 5 mg (7% of theory) of the desired product are obtained.

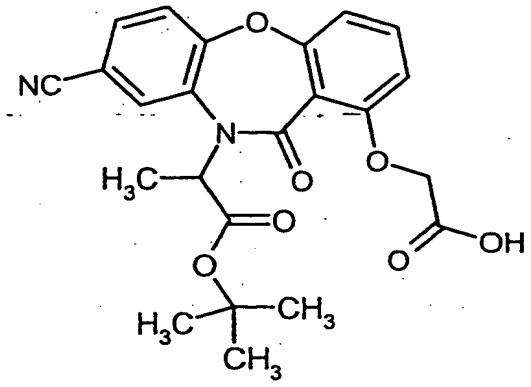
LC-MS (method 4): R_t = 2.82 min,

MS (ESI): m/z = 425 $(M+H)^+$.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.93, 1.03 (2xs, 9H), 1.46 (m, 2H), 3.70 (m, 1H), 4.18 (m, 1H), 4.48 (m, 1H), 4.83 (s, 2H), 6.88 (d, 1H), 6.98 (d, 1H), 7.30 – 7.65 (m, 3H), 8.24 (s, 1H).

Example 28

(R,S)-{[10-(2-tert-Butoxy-1-methyl-2-oxoethyl)-8-cyano-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



Preparation takes place in analogy to Example 25 from 40 mg (0.09 mmol) of the compound from Example 69A. The crude product is chromatographed on silica gel (cyclohexane:ethyl acetate 1:1). 35 mg (88% of theory) of the product are obtained.

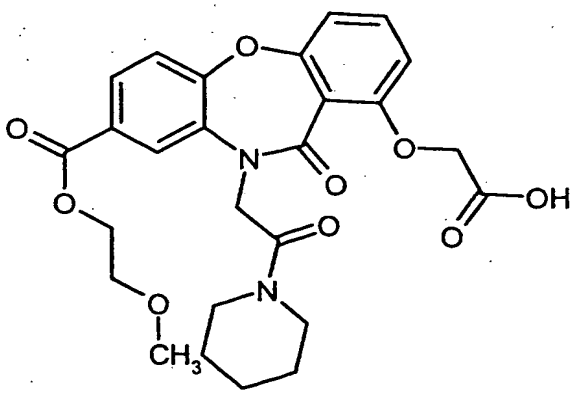
LC-MS (method 7): R_t = 2.99 min,

MS (ESI): m/z = 439 $(M+H)^+$.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 9H), 1.67 (d, 3H), 4.52 (s, 2H), 4.62, 4.90 (2xq, 1H), 6.75 (d, 1H), 6.96 (d, 1H), 7.40 (dd, 1H), 7.58 (m, 1H), 7.74 (m, 1H), 7.88, 7.93 (2xs, 1H).

Example 29

({8-[(2-Methoxyethoxy)carbonyl]-11-oxo-10-[2-oxo-2-(1-piperidinyl)ethyl]-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl}oxy)acetic acid



40.0 mg (0.066 mmol) of 2-methoxyethyl 1-[2-(benzyloxy)-2-oxoethoxy]-11-oxo-10-[2-oxo-2-(1-piperidinyl)ethyl]-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate are dissolved in 4 ml of a 1:1 ethyl acetate/ethanol mixture. 14 mg (0.01 mmol) of 10% palladium on carbon and 25 mg (0.40 mmol) of ammonium formate are added, and the mixture is stirred at 80°C for 3 hours. After the mixture has cooled, the catalyst is filtered off through Celite and washed with ethanol. The solvent is removed in vacuo, the residue is taken up in 5 ml of trichloromethane, and 1 ml of 1N hydrochloric acid is added. Filtration with suction through a sodium sulphate catridge is followed by concentration in vacuo. 34 mg (99% of theory) of the product are obtained.

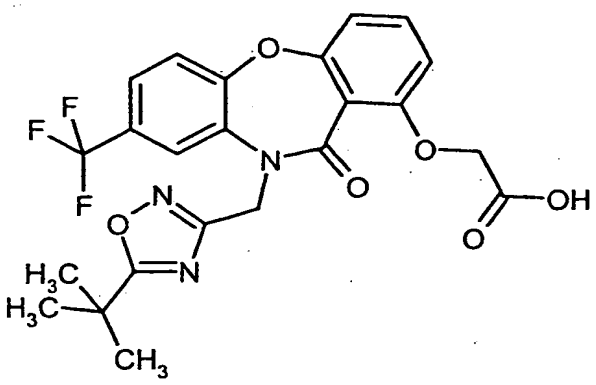
LC-MS (method 7): R_t = 3.22 min

MS (ESIpos): m/z = 513 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.38-1.72 (m, 6 H), 3.11-3.71 (m, 6 H), 4.37 (d, 2 H), 4.58- 5.12 (m, 4 H), 6.79 (d, 1 H), 6.98 (d, 1 H), 7.20 (dd, 1 H), 7.31-7.54 (m, 2 H), 7.78 (dd, 1 H), 7.91 (s, 1H), 13.02 (s_{br}, 1 H)

Example 30

{[10-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)methyl]-11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



80 mg (0.158 mmol) of methyl {[10-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)methyl]-11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetate are dissolved in 8 ml of THF at RT, and 5 mg (0.19 mmol) of lithium hydroxide dissolved in 1 ml of water are added. The reaction mixture is stirred at RT for 3 hours and then purified by preparative HPLC (method 11). 60 mg (77% of theory) of the product are obtained.

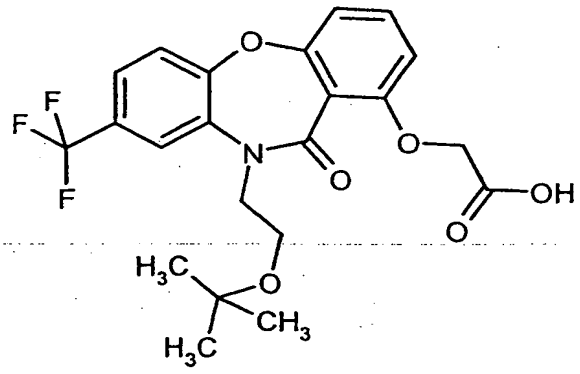
LC-MS (method 2): R_t = 3.80 min

MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.32 (s, 9 H), 4.70 (d, 2 H), 5.40 (dd, 2 H), 6.84 (d, 1 H), 7.02 (d, 1 H), 7.45 (t, 1 H), 7.60 (s, 2 H), 8.10 (s, 1 H), 12.98 (s_{br}, 1 H)

Example 31

{[10-(2-tert-Butoxyethyl)-11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo-[b,f][1,4]-oxazepin-1-yl]oxy}acetic acid



32 mg (0.07 mmol) of methyl {[10-(2-tert-butoxyethyl)-11-oxo-8-(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetate are dissolved in 5 ml of THF at RT, and 2 mg (0.08 mmol) of lithium hydroxide dissolved in 1 ml of water are added. The reaction mixture is stirred at RT for 1 hour and then purified by preparative HPLC (method 11). 26 mg (83% of theory) of the product are obtained.

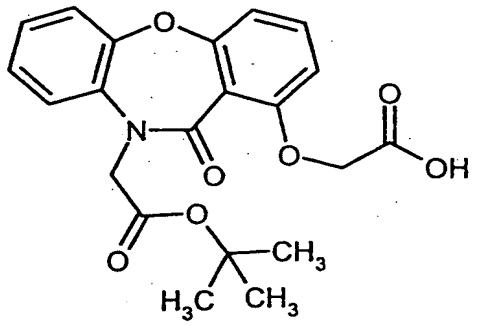
LC-MS (method 7): R_t = 3.50 min

MS (ESIpos): m/z = 454 $(M+H)^+$

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.06 (s, 9 H), 3.39-3.99 (m, 3 H), 4.15-4.35 (m, 1 H), 4.71 (s, 1 H), 6.84 (d, 1 H), 6.98 (d, 1 H), 7.37-7.57 (m, 3 H), 8.33 (s, 1 H), 13.02 (s_{br}, 1 H).

Example 32

{[10-(2-tert-Butoxy-2-oxoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



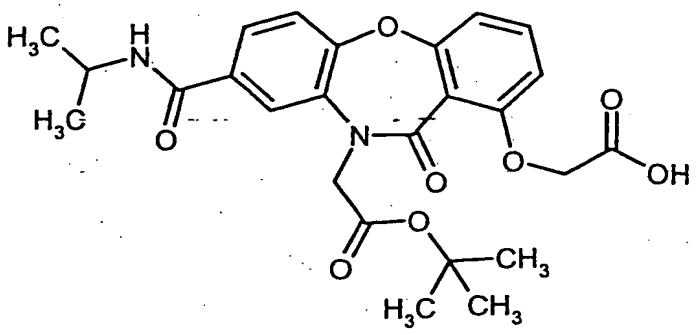
Preparation takes place in analogy to Example 1 with 1-fluoro-2-nitrobenzene as starting material.

MS (ESI): m/z = 400.0 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.37 (s, 9H), 4.54-4.72 (m, 4H), 6.81 (d, 1H), 6.97 (d, 1H), 7.17-7.30 (m, 2H), 7.33-7.45 (m, 3H).

Example 33

({10-(2-tert-Butoxy-2-oxoethyl)-8-[(isopropylamino)carbonyl]-11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepin-1-yl}oxy)acetic acid



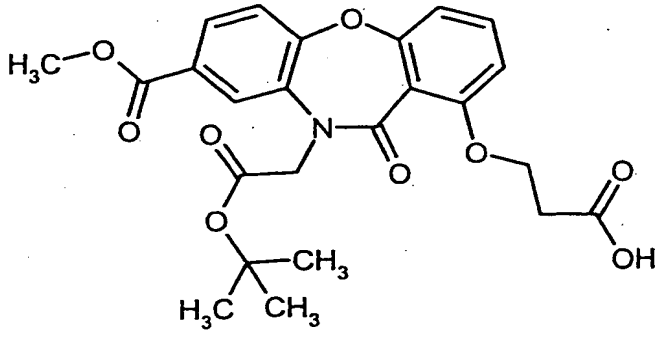
Preparation takes place in analogy to Example 1 with 4-chloro-*N*-*iso*-propyl-3-nitrobenzamide as starting material.

MS (ESI): m/z = 458.2 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.11-1.17 (m, 6H), 1.37 (s, 9H), 4.04. (m_c, 1H), 4.21 (s, 2H), 4.69 (AB signal, 2H), 6.70 (d, 1H), 6.86 (d, 1H), 7.34 (dd, 1H), 7.40 (d, 1H), 7.63 (dd, 1H), 7.78 (d, 1H), 8.20 (d, 1H).

Example 34

3-{[10-(2-tert-Butoxy-2-oxoethyl)-8-(methoxycarbonyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}propionic acid



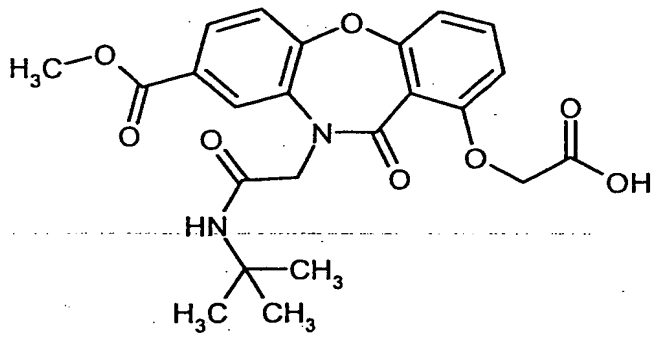
0.10 g (0.25 mmol) of the compound from Example 3A in 3 ml of dimethylformamide is mixed with 20 mg (0.28 mmol) of β-propiolactone and 0.038 mg (0.28 mmol) of potassium carbonate and heated at 60°C for 1 h, and then

stirred at room temperature overnight. A further 20 mg (0.28 mmol) of β-propiolactone are added, and stirring at room temperature is continued for another night. After addition of 10 ml of ethyl acetate and 5 ml of water, the organic phase is extracted with 10 ml of saturated sodium chloride solution. The organic phase is dried over magnesium sulphate and freed of solvent under reduced pressure. The residue is purified by preparative HPLC (method 11) to give 3 mg (3% of theory) of product.

LC-MS (method 3): R_t = 3.6 min,
MS (ESI): m/z = 472.2 $(M+H)^+$.

Example 35

{[10-[2-(tert-Butylamino)-2-oxoethyl]-8-(methoxycarbonyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]oxazepin-1-yl]oxy}acetic acid



1.4 mg of palladium on carbon (0.013 mmol) are added to 14 mg (0.026 mmol) of the compound from Example 78A in 10 ml of tetrahydrofuran, and the mixture is hydrogenated under atmospheric pressure overnight. The catalyst is filtered off with suction through kieselguhr, and 10.5 mg (77% of theory) of product remain.

LC-MS (method 3): R_t = 3.29 min,
MS (ESI): m/z = 457 $[M+H]^+$.

^{1}H-NMR (300 MHz, DMSO-d_6: δ = 1.35 (s, 9H), 3.82 (s, 3H), 4.52 (AB signal, 2H), 4.66 (s, 2H), 6.83 (d, 1H), 6.87 (s, 1H), 7.00 (d, 1H), 7.40-7.49 (m, 2H), 7.96 (s, 1H).

B) Assessment of the physiological activity

The suitability of the compounds according to the invention for the treatment of cardiovascular disorders can be shown in the following assay systems:

Isolation of the soluble form of aminopeptidase N from human plasma

Human blood plasma (Sigma, St. Louis, USA) is fractionated by ammonium sulphate precipitation. More than 80% of the total aminopeptidase N activity is found in the fraction with 50-70% saturation. After centrifugation at 10 000 g, the pellet is resuspended in buffer T (20 mM Tris-HCl, pH 7.5, 2 mM magnesium sulphate, 0.1 M ethylenediaminetetraacetate and 200 mM sodium chloride). The resulting protein solution is again centrifuged at 10 000 g and desalted on a Sephadex G-25 column (Pharmacia Biotech, Uppsala, Sweden). The column is equilibrated with buffer T.

The desalted fraction is loaded onto an affinity chromatography column. The latter is prepared by coupling monoclonal anti-CD13 mouse antibody (Acris SM1070P, Bad Nauheim, Germany) to an N-hydroxysuccinimide-activated HiTrap column (Pharmacia Biotech, Uppsala, Sweden). The column is equilibrated with buffer T.

After sample loading, the column is washed with 5 times the column volume of buffer T. Bound aminopeptidase N is eluted with elution buffer (100 mM glycine and 0.5M sodium chloride, pH 2.5). The eluate is neutralized with Tris-HCl pH 9.0, aliquoted and frozen in liquid nitrogen.

In vitro aminopeptidase N assay

Ala-7-amido-4-methylcoumarin (Bachem, Heidelberg, Germany) is selected as fluorogenic substrate for aminopeptidase N.

The enzymatic activity is measured in a buffer composed of 20 mM MOPS pH 7.0, 100 mM sodium chloride, 5 mM calcium chloride, 0.1% BSA, 25 μM substrate and 1-5 ng/ml aminopeptidase N. The reaction is incubated at a temperature of 37°C in a 384 or 1536 microtitre plate format for 1-3 h. Fluorescence is measured in a Spectra Fluor fluorescence reader (Tecan, Crailsheim, Germany).

Table A shows selected compounds with IC_{50} values.

Table A:

Ex. No.	IC50 [μM]
1	0.015
2	0.034
3	2.2
4	3.9
10	0.001
12	0.045
28	0.002

Migration assay

Human coronary arterial vascular smooth muscle cells (hCAVSMC, 1.5×10^5 cells/well) (TEBU, Offenbach, Germany) are seeded in a 6-well plate and cultivated in M 231 medium (growth medium) (TEBU, Offenbach, Germany) at 37°C/5% carbon dioxide for 48 h. The plates are previously coated with Vitronectin (50 ng/cm^2) (Gibco/Invitrogen, Karlsruhe, Germany). After the incubation time, half the confluent cell monolayer is removed. About 50% of the Vitronectin coating remains in the cell-free region of the well.

The growth medium is replaced by the test medium MCDB-131/0.2% BSA (molecular cellular developmental biology (MCDB); basal medium (BSA))

(Gibco/Invitrogen, Karlsruhe, Germany), and the cells are stimulated with 0.1 U of aminopeptidase N (pig or human) (Sigma, Taufkirchen, Germany).

The test substances are then added in the stated concentrations.
After incubation for 24 and 48 hours, the distance the cells have migrated in the free well area is determined by microscopy.
Each measured point represents a mean of four different regions selected at time 0 h.
PDGF (platelet derived growth factor), a highly potent chemotactic factor for smooth muscle cells, serves as positive control (10 nM) (R&D systems, Wiesbaden-Nordenstadt, Germany).

In vivo assay: mouse model

The test substance is dissolved in a mixture of 5% Transcutol®, 10% Cremophor and 85% physiological saline. Female mice (strain: OF1) (Iffa Credo, L'Arbresle Cedex, France) are treated orally or intravenously with test substance solution. Control mice receive only the solvent. 30 minutes after the intravenous, and 45 minutes after the oral, treatment, all the animals receive 2mg/kg lipopolysaccharide (strain: Salmonella minnesota, manufacturer: Sigma, Steinheim, Germany) by i.p. injection. A blood sample is taken 90 minutes after the i.p. injection. The tumour necrosis factor (TNF) alpha concentration in the serum is determined using a commercial ELISA (manufacturer: R&D, Wiesbaden-Nordenstadt, Germany).

C) **Exemplary embodiments of pharmaceutical compositions**

The substances according to the invention can be converted into pharmaceutical preparations in the following ways:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch, 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. diameter 8 mm, radius of curvature 12 mm.

Production:

A mixture of the compound of Example 1, lactose and starch is granulated with a 5% strength solution (m/m) of PVP in water. The granules are dried and then mixed with magnesium stearate for 5 min. This mixture is compressed using a conventional tablet press (see above for format of the tablet).

Oral suspension:

Composition:

1 000 mg of the compound of Example 1, 1 000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum) (from FMC, USA) and 99 g of water.

A single dose of 100 mg of the compound according to the invention corresponds to 10 ml of oral suspension.

Production:

The Rhodigel is suspended in ethanol, and the compound of Example 1 is added to the suspension. The water is added while stirring. Stirring is continued for about 6 h until the swelling of the Rhodigel is complete.

Solution which can be administered intravenously:

Composition:

1 mg of the compound of Example 1, 15 g of polyethylene glycol 400 and 250 g of water for injections.

Production:

The compound of Example 1 is dissolved together with polyethylene glycol 400 in the water with stirring. The solution is sterilized by filtration (pore diameter 0.22 μm) and dispensed under aseptic conditions into heat-sterilized infusion bottles. The latter are closed with infusion stoppers and crimped caps.